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(54) Title: SUMATRIPTAN CRYSTALLINE FORMS, PHARMACEUTICAL COMPOSITIONS AND METHODS

(57) Abstract: The invention provides novel soluble sumatriptan crystalline forms that include polymorphs, salts, co-crystals and related solvates useful as pharmaceuticals. The invention also provides pharmaceutical compositions comprising, and processes for making, these sumatriptan crystalline forms. Methods of using such compositions for the treatment or prevention of migraine headaches and related neurological disorders are also provided.

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SUMATRIPTAN CRYSTALLINE FORMS, PHARMACEUTICAL COMPOSITIONS AND METHODS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. application 60/449,554, filed February 24, 2003. This application is all hereby incorporated by reference in its entirety, including all figures, formulae, references and tables.

FIELD OF INVENTION

The invention provides novel soluble sumatriptan crystalline forms that include polymorphs, salts, co-crystals and related solvates useful as pharmaceuticals.

The invention also provides pharmaceutical compositions comprising, and processes for making, novel sumatriptan crystalline forms. Methods of using such compositions for the treatment or prevention of migraine headaches and related neurological disorders are also provided. In preferred embodiments, the invention provides novel soluble multicomponent crystalline systems or polymorphs comprising: (a) an organic salt comprising the reaction product of sumatriptan and an organic or inorganic acid.

BACKGROUND OF THE INVENTION

A working definition of migraine is a benign recurring headache and/or neurologic dysfunction, more common in women than men. Classic migraine (migraine with aura) refers to the syndrome of a severe, throbbing headache which often is preceded by sensory, motor or visual symptoms, referred to as an "aura." Common migraine (migraine without aura) denotes a headache without the aura. Common migraine is the most frequent headache type reported by patients.

Migraine attacks may last from four to seventy-two hours and are exacerbated by movement. They are accompanied by nausea and or vomiting or sensitivity to light

and noise, or both. Usually, the pain is one-sided and pulsating. The typical sufferer retreats to a darkened bedroom for the duration of the attack, unless symptoms are relieved by early treatment. A minority (10%) of migraine suffers experience an aura prior to the attack. The migraine aura most commonly consists of visual disturbances or partial loss of vision, but neurological signs such as paresthesias (e.g., a tingling sensation) can also occur.

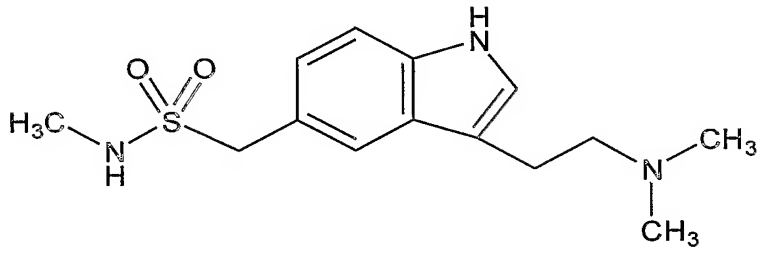
The level of pain and disability associated with migraine can vary greatly. Some migraine suffers can sleep off the attack with the aid of over-the-counter analgesics. Others may be completely disabled for 24 hours or longer, with severe head pain and nausea.

Many drugs are now available for prophylactic treatment of migraine. They must be taken daily. The major drugs for prophylaxis are propanolol, amitriptyline, valproate, verapamil, phenelzine, and methysergide. Use of methysergide carries with it the danger of retroperitoneal fibrosis. Aspirin-like drugs, including aspirin, naproxen, ibuprofen, mefenamic acid, flufenamic acid, and tolfenamic acid are in use as prophylactic agents. The high dosage of these compounds required for effectiveness is a drawback. It has been estimated that the probability of success with any one of the available prophylactic antimigraine drugs is about 60 to 75% (Harrison's Principles of Internal Medicine, eds. Isselbacher et al., McGraw-Hill, Inc., New York, 1994, p. 69). Accordingly, development or identification of drugs for prophylactic treatment of migraine is an area of continuing medical need.

It has been known for some time that sumatriptan, which causes constriction of cranial blood vessels, is an effective treatment for migraine (see, for example, Doenicke et al., Lancet, 1988, Vol. 1, 1309-11; and Feniuk & Humphrey, Drug Development Research, 1992, 26, 235-40). As such, it is the prototypical example of a class of compounds which have recently been classified (Hartig et al.,TIPS, 1996, 17, 103-105) as 5-HT_{1B}/5-HT_{1D} receptor agonists. Activation of 5-HT_{1B} and/or 5-HT_{1D} receptors leads to (1) selective vasoconstriction of certain cranial extracerebral blood

vessel segments; (2) pre-junctional inhibition of the release of proinflammatory neuropeptides from sensory nerve terminals in the meninges; and (3) attenuation of central nociceptive neurotransmission by inhibition of neurotransmitter release within the trigeminal nucleus caudalis.

Sumatriptan succinate is indicated for the acute treatment of migraine attacks with or without aura in adults; it is a selective 5-hydroxytryptamine$_1$ receptor subtype agonist. Sumatriptan succinate is chemically designated as 3-[2-(dimethylamino)ethyl]-N-methyl-indole-5-methanesulfonamide succinate (1:1). Sumatriptan succinate is an acid addition salt of the free base sumatriptan. Sumatriptan has the following structure (1):



(1).

The empirical formula of sumatriptan succinate is $C_{14}H_{21}N_3O_2S \cdot C_4H_6O_4$, representing a molecular weight of 413.5. Sumatriptan succinate is a white to off-white powder that is readily soluble in water and in saline.

In one approved dosage form, sumatriptan succinate is marketed in the United States for oral administration under the trademark IMITREX® in tablets containing 35, 70, or 140 mg of sumatriptan succinate, equivalent to 25, 50, or 100 mg of

sumatriptan, respectively. Liquid oral dosage forms and parenteral dosage forms have also been approved for use in the United States.

Sumatriptan relieves not only the pain of migraine, but also the associated symptoms of nausea, vomiting, light sensitivity (photophobia), and sound sensitivity (phonophobia). Many patients are able to continue to work or return to work after sumatriptan treatment, which often is not possible with ergotamine because of its sedating or nauseating effects.

Given the clinical advantages of sumatriptan, there is a continuing need for new dosage forms of that active ingredient that will facilitate its administration to patients in need and which will be less prone to adverse side effects associated with current sumatriptan products. For example, sumatriptan products that have increased solubility or bioavailability might very well cause fewer cardiovascular adverse incidents than known forms when administered to patients over the age of sixty-five.

SUMMARY OF THE INVENTION

The invention provides novel soluble sumatriptan crystalline forms that include salts, co-crystals, polymorphs, hydrates, and solvates useful as pharmaceuticals. The invention also provides pharmaceutical compositions comprising, and processes for making, these sumatriptan crystalline forms. Methods of using such compositions for the treatment or prevention of migraine headaches and related neurological disorders are also provided. In several embodiments, the invention provides novel soluble crystalline forms comprising: (a) a salt comprising the reaction product of sumatriptan and an organic or inorganic acid; (b) a solvate of sumatriptan or a solvate of a salt of sumatriptan; and (c) a polymorph of sumatriptan or a polymorph of a salt of sumatriptan.

Further, in an embodiment of the invention, two novel sumatriptan succinate polymorphs are characterized by powder X-ray diffraction patterns expressed in terms of 2-theta angles. In another embodiment, the present invention provides a

dichloromethane hemisolvate of sumatriptan succinate characterized by a powder X-ray diffraction pattern expressed in terms of 2-theta angles. In another embodiment, the present invention provides isobutanol, tetrahydrofuran, 1,2-dichloroethane, and dioxane solvates of sumatriptan succinate characterized by powder X-ray diffraction patterns expressed in terms of 2-theta angles.

The invention also provides pharmaceutical compositions comprising, and processes for making, these sumatriptan crystalline forms. Methods of using such compositions for the treatment or prevention of migraines and associated neurological disorders are also provided.

Compounds of the invention include, but are not limited to, soluble crystalline forms, including polymorphs, co-crystals, solvates, and hydrates of sumatriptan succinate, sumatriptan tartrate, sumatriptan citrate, sumatriptan fumarate, sumatriptan malonate, sumatriptan maleate, sumatriptan adipate, sumatriptan di-mesylate, sumatriptan sulfate, sumatriptan benzenesulfonate, or sumatriptan phosphate. Preferred soluble crystalline forms of the invention include dicarboxylic acid salts and hydrochloride acid salts of sumatriptan. Other preferred soluble crystalline forms include phosphoric acid, sulfuric acid or benzenesulfonic acid salts of sumatriptan.

Particularly preferred compounds of the invention include crystalline forms including polymorphs, co-crystals, solvates, and hydrates of sumatriptan succinate, sumatriptan tartrate, sumatriptan fumarate, sumatriptan citrate, sumatriptan malonate, sumatriptan maleate, sumatriptan adipate, or sumatriptan di-mesylate.

The invention further provides methods of treating or preventing migraines or associated neurological disorders in a patient by administration of therapeutically or prophylactically effective amounts of soluble crystalline forms of sumatriptan. Pharmaceutical dosage forms of the invention comprise therapeutically or prophylactically effective amounts of soluble crystalline forms of sumatriptan as disclosed herein.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the PXRD diffractogram of sumatriptan succinate form II.

Figure 2 shows the DSC thermograms of sumatriptan succinate form II ("New Form") and form I ("Stable Form").

Figure 3 shows the TGA thermograms of sumatriptan succinate form II ("New Form") and form I ("Stable Form").

Figure 4 shows the Raman spectra of sumatriptan succinate form II (upper spectrum; "New Form") and form I (lower spectrum; "Stable Form").

Figure 5 shows the PXRD diffractogram of sumatriptan succinate form III.

Figure 6 shows predicted and experimental PXRD diffractograms of sumatriptan succinate form I.

Figures 7A-7C show packing diagrams for sumatriptan succinate form I derived from single-crystal x-ray analysis.

Figure 8 shows the PXRD diffractogram of sumatriptan succinate dichloromethane hemisolvate.

Figure 9 shows the DSC thermograms of sumatriptan succinate dichloromethane hemisolvate (solid line; upper trace) and sumatriptan succinate (form 1; dashed line; lower trace).

Figure 10 shows the TGA thermogram of sumatriptan succinate dichloromethane hemisolvate.

Figure 11 shows the PXRD diffractogram of sumatriptan succinate isobutanol solvate.

Figure 12 shows the PXRD diffractogram of sumatriptan succinate 1,4-dioxane solvate.

Figure 13 shows the PXRD diffractogram of sumatriptan succinate tetrahydrofuran solvate.

Figure 14 shows the PXRD diffractogram of sumatriptan succinate 1,2-dichloroethane solvate.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the following terms have the following respective meanings.

As used herein, the term "solvate" is a complex of variable stoichiometry formed by a solute (sumatriptan or salts, co-crystals, hydrates, or polymorphs of sumatriptan) and an organic solvent as defined herein, including an alcohol.

"Organic or inorganic acids" include, but are not limited to, succinic acid, carboxylic acids, dicarboxylic acids, hydrochloric acid, phosphoric acid, sulfuric acid, benzenesulfonic acid, methanesulfonic acid, and, in general terms, any acidic species that will form a thermodynamically stable crystalline (salt) form upon reaction with the free base sumatriptan.

The term "co-crystal" as used herein means a crystalline material comprised of two or more unique solids at room temperature, each containing distinctive physical characteristics, such as structure, melting point, and heats of fusion, with the exception that, if specifically stated, the API (active pharmaceutical ingredient) may be a liquid at room temperature. The co-crystals of the present invention comprise a co-crystal former H-bonded to sumatriptan or a salt, hydrate, or solvate thereof. The co-crystal former may be H-bonded directly to a soluble crystalline form of the

present invention or may be H-bonded to an additional molecule which is bound to a soluble crystalline form of the present invention. The additional molecule may be H-bonded to a soluble crystalline form or bound ionically or covalently to a soluble crystalline form. The additional molecule could also be a different API. Solvates of soluble crystalline forms of sumatriptan that do not further comprise a co-crystal former are not co-crystals according to the present invention. The co-crystals may however, include one or more solvate molecules in the crystalline lattice. That is, solvates of co-crystals, or a co-crystal further comprising a solvent or compound that is a liquid at room temperature, is included in the present invention, but crystalline material comprised of only a soluble crystalline form of sumatriptan and one or more liquids (at room temperature) are not included in the present invention. Other modes of molecular recognition may also be present including, pi-stacking, guest-host complexation and van der Waals interactions. Of the interactions listed above, hydrogen-bonding is the dominant interaction in the formation of the co-crystal, (and a required interaction according to the present invention) whereby a non-covalent bond is formed between a hydrogen bond donor of one of the moieties and a hydrogen bond acceptor of the other. Hydrogen bonding can result in several different intermolecular configurations. For example, hydrogen bonds can result in the formation of dimers, linear chains, or cyclic structures. These configurations can further include extended (two-dimensional) hydrogen bond networks and isolated triads. An alternative embodiment provides for a co-crystal wherein the co-crystal former is a second API. In another embodiment, the co-crystal former is not an API. For purposes of the present invention, the chemical and physical properties of soluble crystalline forms of sumatriptan in the form of a co-crystal may be compared to a reference compound that is sumatriptan in a different form. The reference compound may be specified as a free form, or more specifically, an anhydrate or hydrate of a free form, or more specifically, for example, a hemihydrate, monohydrate, dihydrate, trihydrate, quadrahydrate, pentahydrate; or a solvate of a free form. For example, the reference compound for sumatriptan succinate co-crystallized with a co-crystal former can be sumatriptan succinate in free form. The reference compound may also be specified as crystalline or amorphous. The reference compound may also be specified as the most stable polymorph of the specified form of the reference compound.

"Soluble crystalline forms" encompass crystalline species including salts, hydrates, solvates, co-crystals or polymorphs that are soluble in aqueous media at values greater than 5 micrograms/mL, more preferably greater than 10 micrograms/mL, more preferably greater than 20 micrograms/mL, more preferably greater than 30 micrograms/mL, more preferably greater than 40 micrograms/mL, more preferably greater than 50 micrograms/mL, and most preferably greater than 100 micrograms/mL in a solution with a pH of about 1. Soluble crystalline forms can comprise: (a) a salt comprising the reaction product of sumatriptan and an organic acid or an inorganic acid; (b) a solvate of sumatriptan or a solvate of a salt of sumatriptan; and (c) a polymorph of sumatriptan or a polymorph of a salt of sumatriptan.

"Organic solvent" includes, but is not limited to, 1,4-dioxane (dioxane), 1,2-dichloroethane, dimethoxyethane, diethylene glycol dimethyl ether, tetrahydrofuran, diisopropyl ether, hydrocarbons such as hexane, heptane, cyclohexane, toluene or xylene, alcohols such as methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol, tert-butanol or ethylene glycol, ketones such as methyl ethyl ketone or isobutyl methyl ketone, amides such as dimethylformamide, dimethylacetamide or N-methylpyrrolidone, and mixtures thereof.

As used herein, the terms "stereoisomer" or "stereoisomeric form" means compounds having a stereoisomeric purity of at least 90%, and preferably at least 95% up to a stereoisomeric purity of 100% by weight, preferably compounds having a stereoisomeric purity of at least 97% up to a stereoisomeric purity of 100%, and more preferably having a stereoisomeric purity of at least 99% up to a stereoisomeric purity of 100% by weight.

As used herein, the term "adjunctively administered" refers to the administration of one or more compounds or active ingredients in addition to a pharmaceutically acceptable crystalline form of sumatriptan, either simultaneously or at intervals prior to, during, or following administration of the pharmaceutically

acceptable salt of sumatriptan to achieve the desired therapeutic or prophylactic effect.

As used herein, the term "pharmaceutically acceptable salt" refers to a salt prepared from pharmacologically acceptable anions, such as, but not limited to, hydrochloride, phosphate, formate, adipate, succinate, fumarate, malate, tartrate, malonate, maleate, mesylate and benzenesulfonate. Particularly preferred anions are tartrate, benzenesulfonate, malate, succinate, hydrobromide, bitartrate, *para*-toluenesulfonate, glycolate, glucuronate, mucate, gentisate, isonicotinate, saccharate, phosphate, hydroiodide, nitrate, sulfate, bisulfate, acetate, propionate, camphorsulfonate, gluconate, isothionate, lactate, furoate, glutamate, ascorbate, benzoate, anthranilate, salicylate, phentylacetate, mandelate, embonate (pamoate), methanesulfonate, ethanesulfonate, pantothenate, stearate, sulfanilate, alginate, p-toluenesulfonate, mesylate, and galacturonate.

As used herein, the term "method of treating or preventing a migraine or associated neurological disorder" means prevention of, or relief from symptoms including a severe, throbbing headache, related sensory, motor or visual symptoms, possibly including an "aura" as well as nausea and or vomiting or sensitivity to light and noise, or both.

In certain embodiments, the novel soluble crystalline forms of sumatriptan have a solubility greater than 5 micrograms/mL, more preferably greater than 10 micrograms/mL, more preferably greater than 20 micrograms/mL, more preferably greater than 30 micrograms/mL, more preferably greater than 40 micrograms/mL, more preferably greater than 50 micrograms/mL, and most preferably greater than 100 micrograms/mL in a solution with a pH of about 1.

Preferred pharmaceutical compositions of the invention comprise a therapeutically effective amount of a novel soluble crystalline form comprising: (a) a salt comprising the reaction product of sumatriptan and an organic or inorganic acid;

(b) a solvate of sumatriptan or a solvate of a salt of sumatriptan; and (c) a polymorph of sumatriptan or a polymorph of a salt of sumatriptan.

A further embodiment of the invention encompasses a method of treating or preventing a migraine or associated neurological disorder in a patient which comprises administering to a patient in need of such treatment or prevention a therapeutically or prophylactically effective amount of a pharmaceutically acceptable soluble crystalline form of sumatriptan. More specifically, the invention includes a method for treating or preventing a migraine or associated neurological disorder in a patient comprising administering to a patient in need of such treatment or prevention, a therapeutically or prophylactically effective amount of a soluble crystalline form of sumatriptan such as sumatriptan succinate, di-mesylate, sumatriptan tartrate, sumatriptan fumarate, sumatriptan malonate, sumatriptan maleate, sumatriptan adipate, or sumatriptan malate.

Sumatriptan succinate is commercially available as a solid dosage form. Sumatriptan succinate, the active ingredient in IMITREX® (marketed by GlaxoSmithKline), is present as a crystalline form herein referred to as form I. Sumatriptan succinate (form I) is described in US Patent No. 5,037,845. The present invention provides novel pharmaceutically acceptable forms of sumatriptan including the succinic acid salt of sumatriptan.

Further, in an embodiment of the invention, two novel sumatriptan succinate polymorphs are characterized by powder X-ray diffraction pattern expressed in terms of 2 theta angles. In another embodiment, the present invention provides a dichloromethane hemisolvate of sumatriptan succinate. In another embodiment, the present invention provides isobutanol, tetrahydrofuran, 1,2-dichloroethane, and dioxane solvates of sumatriptan succinate.

In another embodiment, a method is provided of altering the crystal form of a soluble crystalline form of sumatriptan by changing a parameter selected from the group consisting of vial shape, vial material, cooling rate, vial treatment, mixing rate,

thermal cycling, and dispense method. Vials can be treated with a solvent or a solution such as, but not limited to, acetone or a base solution. Initially, the salt can be dispensed as a solid or as a liquid by dissolving the salt in solution. In another embodiment, a method for altering the crystal form of a soluble crystalline form of sumatriptan comprises altering the size and/or shape of the salt solution container. In another embodiment, a method for altering the crystal form of a soluble crystalline form of sumatriptan comprises increasing the cooling rate of the salt solution. In another embodiment, a method for altering the crystal form of a soluble crystalline form of sumatriptan comprises treating the salt solution container with a solvent or solution. In another embodiment, a method for altering the crystal form of a soluble crystalline form of sumatriptan comprises altering the mixing rate of the salt solution.

Pharmaceutical Compositions and Dosage Forms

Pharmaceutical dosage forms of the invention comprise a therapeutically or prophylactically effective amount of a novel soluble crystalline form of sumatriptan, including hydrates, solvates or polymorphs thereof. These dosage forms also comprise a soluble, multicomponent crystalline system comprising a sumatriptan organic salt. These compositions can be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. Oral and parenteral pharmaceutical compositions and dosage forms are a preferred dosage form. Preferably, the oral dosage form is a solid dosage form, such as a tablet, a caplet, a hard gelatin capsule, a starch capsule, a hydroxypropyl methylcellulose (HPMC) capsule, or a soft elastic gelatin capsule. Other preferred dosage forms include an intradermal dosage form, an intramuscular dosage form, a subcutaneous dosage form, and an intravenous dosage form.

Pharmaceutical compositions and dosage forms of the invention comprise an active ingredient as disclosed herein, e.g., an acid salt such as sumatriptan succinate or a soluble, multicomponent crystalline system comprising a sumatriptan organic salt optionally including an organic solvent. Pharmaceutical compositions and unit dosage forms of the invention typically also comprise one or more pharmaceutically acceptable excipients or diluents. In one embodiment, the pharmaceutical

compositions and unit dosage forms of the invention typically also comprise one or more pharmaceutically acceptable excipients or diluents, wherein at least one of the pharmaceutically acceptable excipients or diluents is an antioxidant.

Pharmaceutical unit dosage forms of this invention are suitable for oral, mucosal (e.g., nasal, sublingual, vaginal, buccal, or rectal), parenteral (e.g., intramuscular, subcutaneous, intravenous, intraarterial, or bolus injection), topical, or transdermal administration to a patient. Examples of dosage forms include, but are not limited to: tablets, caplets, capsules, such as hard gelatin capsules, starch capsules, hydroxypropyl methylcellulose (HPMC) capsules, and soft elastic gelatin capsules, cachets, troches, lozenges, dispersions, suppositories, ointments, cataplasms (poultices), pastes, powders, dressings, creams, plasters, solutions, patches, aerosols (e.g., nasal sprays or inhalers), gels, liquid dosage forms suitable for oral or mucosal administration to a patient, including suspensions (e.g., aqueous or non-aqueous liquid suspensions, oil-in-water emulsions, or water-in-oil liquid emulsions), solutions, and elixirs; liquid dosage forms suitable for parenteral administration to a patient; and sterile solids (e.g., crystalline or amorphous solids) that can be reconstituted to provide liquid dosage forms suitable for parenteral administration to a patient.

The composition, shape, and type of dosage forms of the invention will typically vary depending on their use. For example, a dosage form used in the acute treatment of a disease or disorder may contain larger amounts of the active ingredient than a dosage form used in the chronic treatment of the same disease or disorder. Similarly, a parenteral dosage form may contain smaller amounts of the active ingredient than an oral dosage form used to treat the same disease or disorder. These and other ways in which specific dosage forms encompassed by this invention will vary from one another will be readily apparent to those skilled in the art. See, e.g., Remington's Pharmaceutical Sciences, 18th ed., Mack Publishing, Easton PA (1990) or Remington: The Science and Practice of Pharmacy, 19th ed., Mack Publishing, Easton PA (1995).

Typical pharmaceutical compositions and dosage forms comprise one or more excipients. Suitable excipients are well known to those skilled in the art of pharmacy, and non-limiting examples of suitable excipients are provided herein. Whether a particular excipient is suitable for incorporation into a pharmaceutical composition or dosage form depends on a variety of factors well known in the art including, but not limited to, the way in which the dosage form will be administered to a patient. For example, oral dosage forms such as tablets or capsules may contain excipients not suited for use in parenteral dosage forms. In addition, pharmaceutical compositions or dosage forms may contain one or more compounds that reduce or alter the rate by which the active ingredient will decompose. Such compounds, which are referred to herein as "stabilizers", include, but are not limited to, antioxidants, pH buffers, or salt buffers.

One or more antioxidants can be used in pharmaceutical compositions and dosage forms to deter radical oxidation of the active ingredient, wherein such antioxidants include, but are not limited to, ascorbic acid, phenolic antioxidants including, but not limited to, butylated hydroxyanisole (BHA) and propyl gallate, and chelators including, but not limited to citrate, EDTA, and DTPA. Preferably, in cases where radical oxidation of the active ingredient is known to occur, a combination of phenolic antioxidants and chelators can be used.

Like the amounts and types of excipients, the amounts and specific type of active ingredient in a dosage form may differ depending on factors such as, but not limited to, the route by which it is to be administered to patients. However, typical dosage forms of the invention comprise a pharmaceutically acceptable soluble crystalline form of sumatriptan or its stereoisomers, selected from the group consisting of sumatriptan succinate and sumatriptan-HCl, and pharmaceutically acceptable hydrates, solvates, polymorphs, and co-crystals thereof, in an amount ranging from about 10 mg to about 1000 mg, preferably in an amount ranging from about 25 mg to about 500 mg, more preferably in an amount of from 40 mg to 400 mg, and most preferably in an amount of from about 50 mg to about 200 mg.

Oral Dosage Forms

Pharmaceutical compositions of the invention that are suitable for oral administration can be presented as discrete dosage forms, such as, but not limited to, tablets (including without limitation scored or coated tablets), pills, caplets, capsules (including without limitation hard gelatin capsules, starch capsules, HPMC capsules, and soft elastic gelatin capsules), chewable tablets, powder packets, sachets, troches, wafers, aerosol sprays, or liquids, such as but not limited to, syrups, elixirs, solutions or suspensions in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil emulsion. Such compositions contain a predetermined amount of the active ingredient, and may be prepared by methods of pharmacy well known to those skilled in the art. See generally, Remington's Pharmaceutical Sciences, 18th ed., Mack Publishing, Easton, PA (1990) or Remington: The Science and Practice of Pharmacy, 19th ed., Mack Publishing, Easton, PA (1995).

Typical oral dosage forms of the invention are prepared by combining the active ingredient in an intimate admixture with at least one excipient according to conventional pharmaceutical compounding techniques. Excipients can take a wide variety of forms depending on the form of the composition desired for administration. For example, excipients suitable for use in oral liquid or aerosol dosage forms include, but are not limited to, water, glycols, oils, alcohols, flavoring agents, preservatives, and coloring agents. Examples of excipients suitable for use in solid oral dosage forms (e.g., powders, tablets, capsules, and caplets) include, but are not limited to, starches, sugars, microcrystalline cellulose, kaolin, diluents, granulating agents, lubricants, binders, stabilizers, and disintegrating agents.

Due to their ease of administration, tablets, caplets, and capsules (such as hard gelatin, HPMC, or starch capsules) represent the most advantageous solid oral dosage unit forms, in which case solid pharmaceutical excipients are used. If desired, tablets or caplets can be coated by standard aqueous or nonaqueous techniques. These dosage forms can be prepared by any of the methods of pharmacy. In general, pharmaceutical compositions and dosage forms are prepared by uniformly and intimately admixing the active ingredient(s) with liquid carriers, finely divided solid

carriers, or both, and then shaping the product into the desired presentation if necessary.

For example, a tablet can be prepared by compression or molding. Compressed tablets can be prepared by compressing in a suitable machine the active ingredient(s) in a free-flowing form, such as a powder or granules, optionally mixed with one or more excipients. Molded tablets can be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

Examples of excipients that can be used in oral dosage forms of the invention include, but are not limited to, binders, stabilizers, fillers, disintegrants, and lubricants. Binders suitable for use in pharmaceutical compositions and dosage forms include, but are not limited to, corn starch, potato starch, or other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (e.g., ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch, hydroxypropyl methyl cellulose, (e.g., Nos. 2208, 2906, 2910), microcrystalline cellulose, and mixtures thereof.

Suitable forms of microcrystalline cellulose include, but are not limited to, the materials sold as AVICEL-PH-101, AVICEL-PH-103, AVICEL RC-581, and AVICEL-PH-105 (available from FMC Corporation, American Viscose Division, Avicel Sales, Marcus Hook, PA, U.S.A.), and mixtures thereof. An exemplary suitable binder is a mixture of microcrystalline cellulose and sodium carboxymethyl cellulose sold as AVICEL RC-581. Suitable anhydrous or low moisture excipients or additives include AVICEL-PH-103™ and Starch 1500 LM.

Examples of fillers suitable for use in the pharmaceutical compositions and dosage forms disclosed herein include, but are not limited to, talc, calcium carbonate (e.g., granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures

thereof. The binder or filler in pharmaceutical compositions of the invention is typically present in from about 50 to about 99 weight percent of the pharmaceutical composition or dosage form.

Disintegrants can be used in the pharmaceutical compositions and dosage forms to provide tablets or caplets that disintegrate when exposed to an aqueous environment. Tablets or caplets that contain too much disintegrant may disintegrate in storage, while those that contain too little may be insufficient for disintegration to occur and may thus alter the rate and extent of release of the active ingredient(s) from the dosage form. Thus, a sufficient amount of disintegrant that is neither too little nor too much to control the release of the active ingredient(s) should be used to form solid oral dosage forms of the invention. The amount of disintegrant used varies based upon the type of formulation and mode of administration, and is readily discernible to those of ordinary skill in the art. Typical pharmaceutical compositions comprise from about 0.5 to about 15 weight percent of disintegrant, preferably from about 1 to about 5 weight percent of disintegrant.

Disintegrants that can be used to form pharmaceutical compositions and dosage forms of the invention include, but are not limited to, agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, other starches, pre-gelatinized starch, clays, other algins, other celluloses, gums, and mixtures thereof.

Antioxidants can be used in the pharmaceutical compositions and dosage forms to deter degradation or radical oxidation of the active ingredient. Examples of suitable antioxidants include, but are not limited to, ascorbic acid, phenolic antioxidants including, but not limited to, butylated hydroxyanisole (BHA) and propyl gallate, and chelators including, but not limited to, citrate, EDTA, and DTPA, or combinations thereof.

Lubricants that can be used to form pharmaceutical compositions and dosage forms of the invention include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (e.g., peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethyl laureate, agar, and mixtures thereof. Additional lubricants include, for example, a syloid silica gel (AEROSIL 200, manufactured by W.R. Grace Co. of Baltimore, MD), a coagulated aerosol of synthetic silica (marketed by Degussa Co. of Plano, TX), CAB-O-SIL (a pyrogenic silicon dioxide product sold by Cabot Co. of Boston, MA), and mixtures thereof. If used at all, lubricants are typically used in an amount of less than about 1 weight percent of the pharmaceutical compositions or dosage forms into which they are incorporated.

Other oral dosage forms for pharmaceutical compositions of the invention are soft elastic gelatin capsules. Soft elastic gelatin capsule unit dosage forms can be made using conventional methods well known in the art. See, e.g., Ebert, Pharm. Tech, 1(5):44-50 (1977). In general, soft elastic gelatin capsules (also known as soft gels) have an elastic or soft, globular or oval shaped gelatin shell that is typically a bit thicker than that of hard gelatin capsules, wherein a plasticizing agent, e.g., glycerin, sorbitol, or a similar polyol, is added to a gelatin. The type of gelatin, as well as the amounts of plasticizer and water, can be used to vary the hardness of the capsule shell. The soft gelatin shells may contain a preservative, such as methyl- and propylparabens and sorbic acid, to prevent the growth of fungi. The active ingredient may be dissolved or suspended in a liquid vehicle or carrier, such as vegetable or mineral oils, glycols, such as polyethylene glycol and propylene glycol, triglycerides, surfactants, such as polysorbates, or a combination thereof.

Controlled Release Dosage Forms

Pharmaceutically acceptable soluble crystalline forms of sumatriptan can be administered by controlled- or delayed-release means. Controlled-release pharmaceutical products have a common goal of improving drug therapy over that achieved by their non-controlled release counterparts. Ideally, the use of an optimally designed controlled-release preparation in medical treatment is characterized by a minimum of drug substance being employed to cure or control the condition in a minimum amount of time. Advantages of controlled-release formulations include: 1) extended activity of the drug; 2) reduced dosage frequency; 3) increased patient compliance; 4) usage of less total drug; 5) reduction in local or systemic side effects; 6) minimization of drug accumulation; 7) reduction in blood level fluctuations; 8) improvement in efficacy of treatment; 9) reduction of potentiation or loss of drug activity; and 10) improvement in speed of control of diseases or conditions. (Kim, Cherng-ju, Controlled Release Dosage Form Design, 2 Technomic Publishing, Lancaster, Pa.: 2000).

Conventional dosage forms generally provide rapid or immediate drug release from the formulation. Depending on the pharmacology and pharmacokinetics of the drug, use of conventional dosage forms can lead to wide fluctuations in the concentrations of the drug in a patient's blood and other tissues. These fluctuations can impact a number of parameters, such as dose frequency, onset of action, duration of efficacy, maintenance of therapeutic blood levels, toxicity, side effects, and the like. Advantageously, controlled-release formulations can be used to control a drug's onset of action, duration of action, plasma levels within the therapeutic window, and peak blood levels. In particular, controlled- or extended-release dosage forms or formulations can be used to ensure that the maximum effectiveness of a drug is achieved while minimizing potential adverse effects and safety concerns, which can occur both from under dosing a drug (i.e., going below the minimum therapeutic levels) as well as exceeding the toxicity level for the drug.

Most controlled-release formulations are designed to initially release an amount of drug (active ingredient) that promptly produces the desired therapeutic

effect, and gradually and continually release other amounts of drug to maintain this level of therapeutic or prophylactic effect over an extended period of time. In order to maintain this constant level of drug in the body, the drug must be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body. Controlled-release of an active ingredient can be stimulated by various conditions including, but not limited to, pH, ionic strength, osmotic pressure, temperature, enzymes, water, and other physiological conditions or compounds.

A variety of known controlled- or extended-release dosage forms, formulations, and devices can be adapted for use with the soluble crystalline forms and compositions of the invention. Examples include, but are not limited to, those described in U.S. Pat. Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; 4,008,719; 5,674,533; 5,059,595; 5,591,767; 5,120,548; 5,073,543; 5,639,476; 5,354,556; 5,733,566; and 6,365,185 B1; each of which is incorporated herein by reference. These dosage forms can be used to provide slow or controlled-release of one or more active ingredients using, for example, hydroxypropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems (such as OROS® (Alza Corporation, Mountain View, Calif. USA)), multilayer coatings, microparticles, liposomes, or microspheres or a combination thereof to provide the desired release profile in varying proportions. Additionally, ion exchange materials can be used to prepare immobilized, adsorbed soluble crystalline forms and thus effect controlled delivery of the drug. Examples of specific anion exchangers include, but are not limited to, Duolite® A568 and Duolite® AP143 (Rohm & Haas, Spring House, PA. USA).

One embodiment of the invention encompasses a unit dosage form which comprises a pharmaceutically acceptable soluble crystalline form of sumatriptan (e.g., sumatriptan succinate), and one or more pharmaceutically acceptable excipients or diluents, wherein the pharmaceutical composition or dosage form is formulated for controlled-release. Specific dosage forms utilize an osmotic drug delivery system.

A particular and well-known osmotic drug delivery system is referred to as OROS® (Alza Corporation, Mountain View, Calif. USA). This technology can readily be adapted for the delivery of compounds and compositions of the invention. Various aspects of the technology are disclosed in U.S. Pat. Nos. 6,375,978 B1; 6,368,626 B1; 6,342,249 B1; 6,333,050 B2; 6,287,295 B1; 6,283,953 B1; 6,270,787 B1; 6,245,357 B1; and 6,132,420; each of which is incorporated herein by reference. Specific adaptations of OROS® that can be used to administer compounds and compositions of the invention include, but are not limited to, the OROS® Push-Pull™, Delayed Push-Pull™, Multi-Layer Push-Pull™, and Push-Stick™ Systems, all of which are well known. See, e.g., http://www.alza.com. Additional OROS® systems that can be used for the controlled oral delivery of compounds and compositions of the invention include OROS®-CT and L-OROS®. Id.; see also, Delivery Times, vol. II, issue II (Alza Corporation).

Conventional OROS® oral dosage forms are made by compressing a drug powder (e.g., sumatriptan succinate) into a hard tablet, coating the tablet with cellulose derivatives to form a semi-permeable membrane, and then drilling an orifice in the coating (e.g., with a laser). (Kim, Cherng-ju, Controlled Release Dosage Form Design, 231-238 Technomic Publishing, Lancaster, Pa.: 2000). The advantage of such dosage forms is that the delivery rate of the drug is not influenced by physiological or experimental conditions. Even a drug with a pH-dependent solubility can be delivered at a constant rate regardless of the pH of the delivery medium. But because these advantages are provided by a build-up of osmotic pressure within the dosage form after administration, conventional OROS® drug delivery systems cannot be used to effectively deliver drugs with low water solubility.

A specific dosage form of the invention comprises: a wall defining a cavity, the wall having an exit orifice formed or formable therein and at least a portion of the wall being semipermeable; an expandable layer located within the cavity remote from the exit orifice and in fluid communication with the semipermeable portion of the wall; a dry or substantially dry state drug layer located within the cavity adjacent to the exit orifice and in direct or indirect contacting relationship with the expandable

layer; and a flow-promoting layer interposed between the inner surface of the wall and at least the external surface of the drug layer located within the cavity, wherein the drug layer comprises a soluble crystalline form of the present invention. See U.S. Pat. No. 6,368,626, the entirety of which is incorporated herein by reference.

Another specific dosage form of the invention comprises: a wall defining a cavity, the wall having an exit orifice formed or formable therein and at least a portion of the wall being semipermeable; an expandable layer located within the cavity remote from the exit orifice and in fluid communication with the semipermeable portion of the wall; a drug layer located within the cavity adjacent the exit orifice and in direct or indirect contacting relationship with the expandable layer; the drug layer comprising a liquid, active agent formulation absorbed in porous particles, the porous particles being adapted to resist compaction forces sufficient to form a compacted drug layer without significant exudation of the liquid, active agent formulation, the dosage form optionally having a placebo layer between the exit orifice and the drug layer, wherein the active agent formulation comprises a soluble crystalline form of sumatriptan. See U.S. Pat. No. 6,342,249, the entirety of which is incorporated herein by reference.

Topical Dosage Forms

Topical dosage forms of the invention include, but are not limited to, creams, lotions, ointments, gels, shampoos, sprays, aerosols, solutions, emulsions, and other forms know to one of skill in the art. See, e.g., Remington's Pharmaceutical Sciences, 18th ed., Mack Publishing, Easton, PA (1990); and Introduction to Pharmaceutical Dosage Forms, 4th ed., Lea & Febiger, Philadelphia, PA (1985). For non-sprayable topical dosage forms, viscous to semi-solid or solid forms comprising a carrier or one or more excipients compatible with topical application and having a dynamic viscosity preferably greater than water are typically employed. Suitable formulations include, without limitation, solutions, suspensions, emulsions, creams, ointments, powders, liniments, salves, and the like, which are, if desired, sterilized or mixed with auxiliary agents (e.g., preservatives, stabilizers, wetting agents, buffers, or salts) for influencing various properties, such as, for example, osmotic pressure. Other suitable

topical dosage forms include sprayable aerosol preparations wherein the active ingredient, preferably in combination with a solid or liquid inert carrier, is packaged in a mixture with a pressurized volatile (e.g., a gaseous propellant, such as freon), or in a squeeze bottle. Moisturizers or humectants can also be added to pharmaceutical compositions and dosage forms if desired. Examples of such additional ingredients are well known in the art. See, e.g., Remington's Pharmaceutical Sciences, 18th ed., Mack Publishing, Easton, PA (1990).

Parenteral Dosage Forms

Parenteral dosage forms can be administered to patients by various routes, including, but not limited to, subcutaneous, intravenous (including bolus injection), intramuscular, and intraarterial. Since administration of parenteral dosage forms typically bypasses the patient's natural defenses against contaminants, parenteral dosage forms are preferably sterile or capable of being sterilized prior to administration to a patient. Examples of parenteral dosage forms include, but are not limited to, solutions ready for injection, dry products ready to be dissolved or suspended in a pharmaceutically acceptable vehicle for injection, suspensions ready for injection, and emulsions.

Suitable vehicles that can be used to provide parenteral dosage forms of the invention are well known to those skilled in the art. Examples include, without limitation: sterile water; Water for Injection USP; saline solution; glucose solution; aqueous vehicles such as but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and propylene glycol; and non-aqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate. The solutions are preferably isotonic and have a physiological pH.

Compounds that increase the solubility of the active ingredient(s) disclosed herein can also be incorporated into the parenteral dosage forms of the invention.

Transdermal and Mucosal Dosage Forms

Transdermal and mucosal dosage forms of the invention include, but are not limited to, ophthalmic solutions, patches, sprays, aerosols, creams, lotions, suppositories, ointments, gels, solutions, emulsions, suspensions, or other forms know to one of skill in the art. See, e.g., Remington's Pharmaceutical Sciences, 18th ed., Mack Publishing, Easton, PA (1990); and Introduction to Pharmaceutical Dosage Forms, 4th ed., Lea & Febiger, Philadelphia, PA (1985). Dosage forms suitable for treating mucosal tissues within the oral cavity can be formulated as mouthwashes, as oral gels, or as buccal patches. Further, transdermal dosage forms include "reservoir type" or "matrix type" patches, which can be applied to the skin and worn for a specific period of time to permit the penetration of a desired amount of active ingredient.

Suitable excipients (e.g., carriers and diluents) and other materials that can be used to provide transdermal and mucosal dosage forms encompassed by this invention are well known to those skilled in the pharmaceutical arts, and depend on the particular tissue or organ to which a given pharmaceutical composition or dosage form will be applied. With that fact in mind, typical excipients include, but are not limited to water, acetone, ethanol, ethylene glycol, propylene glycol, butane-1,3-diol, isopropyl myristate, isopropyl palmitate, mineral oil, and mixtures thereof, to form dosage forms that are non-toxic and pharmaceutically acceptable.

Depending on the specific tissue to be treated, additional components may be used prior to, in conjunction with, or subsequent to treatment with active ingredients of the invention. For example, penetration enhancers can be used to assist in delivering the active ingredients to or across the tissue. Suitable penetration enhancers include, but are not limited to: acetone; various alcohols such as ethanol, oleyl, an tetrahydrofuryl; alkyl sulfoxides such as dimethyl sulfoxide; dimethyl acetamide; dimethyl formamide; polyethylene glycol; pyrrolidones such as polyvinylpyrrolidone; Kollidon grades (Povidone, Polyvidone); urea; and various

water-soluble or insoluble sugar esters such as TWEEN 80 (polysorbate 80) and SPAN 60 (sorbitan monostearate).

The pH of a pharmaceutical composition or dosage form, or of the tissue to which the pharmaceutical composition or dosage form is applied, may also be adjusted to improve delivery of the active ingredient(s). Similarly, the polarity of a solvent carrier, its ionic strength, or tonicity can be adjusted to improve delivery. Compounds such as stearates can also be added to pharmaceutical compositions or dosage forms to advantageously alter the hydrophilicity or lipophilicity of the active ingredient(s) so as to improve delivery. In this regard, stearates can serve as a lipid vehicle for the formulation, as an emulsifying agent or surfactant, and as a delivery-enhancing or penetration-enhancing agent. Different hydrates, solvates, polymorphs, or co-crystals of the active ingredient can be used to further adjust the properties of the resulting composition.

In another embodiment, the present invention provides a combination oral dosage form and transdermal dosage from of a soluble crystalline form of sumatriptan. This embodiment provides an initial rapid onset for acute migraine treatment followed by a level of sustained release to prevent or decrease the reoccurrence of migraine. In one embodiment, the blood plasma concentration of a soluble crystalline form of sumatriptan released in a sustained manner is less than that of the initially released therapeutic agent. In another embodiment, the blood plasma concentration of a soluble crystalline form of sumatriptan released in a sustained manner is about equal to that of the initially released therapeutic agent.

Methods Of Treatment and Prevention

Pharmaceutically acceptable salts, co-crystals, and polymorphs of sumatriptan, and pharmaceutical compositions and dosage forms thereof, should possess potent activity against, and are useful for treating or preventing, a migraine or associated neurological disorder. For example, pharmaceutically acceptable soluble crystalline form of sumatriptan, and pharmaceutical compositions and dosage forms thereof, can be used to treat or prevent a severe, throbbing headache, related sensory, motor or

visual symptoms, including an "aura" as well as nausea and or vomiting or sensitivity to light and noise, or both.

The magnitude of a prophylactic or therapeutic dose of each active ingredient in the acute or chronic management of a disease or disorder will vary with the disease or disorder itself, the specific active ingredients, and the route of administration. The dose, dose frequency, or both, may also vary according to age, body weight, response, the past medical history of the patient, and consideration of whether the patient is or will be concurrently or concomitantly taking other drugs or pharmaceuticals. Suitable dosing regimens can be readily selected by the skilled artisan with due consideration of such factors by following, for example, dosages and dose regimens reported in the literature and recommended in the Physician's Desk Reference® (56^{th} ed., 2002) for itraconazole. Unless otherwise indicated, the magnitude of a prophylactic or therapeutic dose of the active ingredient used in an embodiment of the invention will be that which is safe and effective (e.g., has received regulatory approval).

In one embodiment of the invention, the active ingredient (e.g., soluble crystalline forms of sumatriptan succinate, sumatriptan di-mesylate, sumatriptan tartrate, sumatriptan fumarate, sumatriptan malonate, sumatriptan maleate, sumatriptan adipate, sumatriptan malate, sumatriptan-HCl, sumatriptan phosphate, sumatriptan sulfate or sumatriptan benzenesulfonate, or multicomponent crystalline systems, hydrates, solvates, polymorphs, or co-crystals thereof) is administered orally as needed in an amount of from about 10 mg to about 1000 mg, preferably in an amount of from about 25 mg to about 500 mg, more preferably in an amount from about 40 mg to about 400 mg, and most preferably in an amount of from about 50 mg to about 200 mg. The dosage amounts can be administered in single or divided doses. The dosage amounts and frequencies provided above are encompassed by the terms "therapeutically effective", "prophylactically effective", and "therapeutically or prophylactically effective" as used herein.

The suitability of a particular route of administration employed for a particular active ingredient will depend on the active ingredient itself (e.g., whether it can be

administered orally without decomposing prior to entering the blood stream) and the disease or disorder to be treated or prevented. For example, oral or parenteral administration is typically preferred for treating or preventing a severe, throbbing headache, related sensory, motor or visual symptoms, including an "aura", as well as nausea and or vomiting or sensitivity to light and noise, or both. Similarly, oral or parenteral administration may be preferred for the treatment or prevention of migraine, whereas transdermal or subcutaneous routes of administration may be employed for treatment or prevention of chronic migraines or associated disorders.

Preparation of sumatriptan and related pharmaceutically acceptable salts

Sumatriptan and related pharmaceutically acceptable salts can be made using various methods known to those skilled in the art. Processes for making sumatriptan and related pharmaceutically acceptable salts are disclosed in United States Patent Nos. 4,816,470 and 5,037,845, the complete disclosures of which are hereby incorporated by reference.

Salts, co-crystals, or organic salts of sumatriptan, including without limitation, pharmaceutically acceptable salts can be prepared by treating sumatriptan free base with appropriate acids, such as organic or inorganic acids, including without limitation, succinic acid, malic acid, hydrochloric acid, sulfuric acid, fumaric acid, phosphoric acid, tartaric acid, maleic acid, malonic acid, adipic acid, benzenesulfonic acid, and the like. For example, the process for forming a salt and co-crystal can be carried out in a solvent system in which both reactants (i.e., sumatriptan free base and the respective acid) are sufficiently soluble.

In one method, in order to achieve crystallization or precipitation, a solvent or solvent mixture in which the resulting salt and co-crystal is only slightly soluble or not soluble at all is used. Alternatively, supersaturated solutions of sumatriptan succinate may be prepared by increasing the temperature of the solvent mixture in the presence of sumatriptan succinate, then decreasing the temperature; forms of sumatriptan succinate will then recrystallize spontaneously. Alternatively, a solvent in which the desired salt and co-crystal is very soluble can be used, and then an anti-

solvent (or a solvent in which the resulting salt is poorly soluble) is added to the solution. Other variants for salt formation or crystallization include concentrating the salt and co-crystal solution (e.g., by heating, under reduced pressure if necessary, or by slowly evaporating the solvent, for example, at room temperature), or seeding with the addition of seed crystals, or setting up water activity required for hydrate formation.

The invention is further defined by reference to the following examples. It will be apparent to those skilled in the art that many modifications, both to materials and methods, can be practiced without departing from the scope of this invention.

EXEMPLIFICATION

Analytical Methods

Procedure for DSC analysis

DSC analysis of the samples was performed using a Q1000 Differential Scanning Calorimeter (TA Instruments, New Castle, DE, U.S.A.), which uses Advantage for QW-Series, version 1.0.0.78, Thermal Advantage Release 2.0 (2001 TA Instruments-Water LLC). In addition, the analysis software used was Universal Analysis 2000 for Windows 95/95/2000/NT, version 3.1E;Build 3.1.0.40 (2001 TA Instruments-Water LLC).

For the DSC analysis, the purge gas used was dry nitrogen, the reference material was an empty aluminum pan that was crimped, and the sample purge was 50 mL/minute.

DSC analysis of the sample was performed by placing ≤ 2 mg of sample in an aluminum pan with a crimped pan closure. The starting temperature was typically 20 degrees C with a heating rate of 10 degrees C/minute, and the ending temperature was 300 degrees C. Unless otherwise indicated, all reported transitions are as stated +/- 1.0 degrees C.

Procedure for TGA analysis

TGA analysis of samples was performed using a Q500 Thermogravimetric Analyzer (TA Instruments, New Castle, DE, U.S.A.), which uses Advantage for QW-Series, version 1.0.0.78, Thermal Advantage Release 2.0 (2001 TA Instruments-Water LLC). In addition, the analysis software used was Universal Analysis 2000 for Windows 95/95/2000/NT, version 3.1E;Build 3.1.0.40 (2001 TA Instruments-Water LLC).

For all of the TGA experiments, the purge gas used was dry nitrogen, the balance purge was 40 mL/minute N_2, and the sample purge was 60 mL/minute N_2.

TGA of the sample was performed by placing ≤ 2 mg of sample in a platinum pan. The starting temperature was typically 20 degrees C with a heating rate of 10 degrees C/minute, and the ending temperature was 300 degrees C.

Procedure for PXRD analysis

A powder X-ray diffraction pattern for the samples was obtained using a D/Max Rapid, Contact (Rigaku/MSC, The Woodlands, TX, U.S.A.), which uses as its control software RINT Rapid Control software, Rigaku Rapid/XRD, version 1.0.0 (1999 Rigaku Co.). In addition, the analysis software used were RINT Rapid display software, version 1.18 (Rigaku/MSC), and JADE XRD Pattern Processing, versions 5.0 and 6.0 ((1995-2002, Materials Data, Inc.).

For the PXRD analysis, the acquisition parameters were as follows: source was Cu with a K line at 1.5406Å; x-y stage was manual; collimator size was 0.3 or 0.8 mm; capillary tube (Charles Supper Company, Natick, MA, U.S.A.) was 0.3 mm ID; reflection mode was used; the power to the X-ray tube was 46 kV; the current to the X-ray tube was 40 mA; the omega-axis was oscillating in a range of 0-5 degrees at a speed of 1 degree/minute; the phi-axis was spinning at an angle of 360 degrees at a speed of 2 degrees/second; 0.3 or 0.8 mm collimator; the collection time was 60 minutes; the temperature was room temperature; and the heater was not used. The sample was presented to the X-ray source in a boron rich glass capillary.

In addition, the analysis parameters were as follows: the integration 2-theta range was 2-40 or 60 degrees; the integration chi range was 0-360 degrees; the number of chi segments was 1; the step size used was 0.02; the integration utility was cylint; normalization was used; dark counts were 8; omega offset was 180; and chi and phi offsets were 0.

The relative intensity of peaks in a diffractogram is not necessarily a limitation of the PXRD pattern because peak intensity can vary from sample to sample, e.g., due to crystalline impurities. Further, the angles of each peak can vary by about +/- 0.1 degrees, preferably +/-0.05. The entire pattern or most of the pattern peaks may also shift by about +/- 0.1 degree due to differences in calibration, settings, and other variations from instrument to instrument and from operator to operator.

Procedure for Raman Acquisition, Filtering and Binning

Acquisition

The sample was either left in the glass vial in which it was processed or an aliquot of the sample was transferred to a glass slide. The glass vial or slide was positioned in the sample chamber. The measurement was made using an Almega™ Dispersive Raman (Almega™ Dispersive Raman, Thermo-Nicolet, 5225 Verona Road, Madison, WI 53711-4495) system fitted with a 785nm laser source. The sample was manually brought into focus using the microscope portion of the apparatus with a 10x power objective (unless otherwise noted), thus directing the laser onto the surface of the sample. The spectrum was acquired using the parameters outlined in Table I. (Exposure times and number of exposures may vary; changes to parameters will be indicated for each acquisition.)

Filtering and Binning

Each spectrum in a set was filtered using a matched filter of feature size 25 to remove background signals, including glass contributions and sample fluorescence. This is particularly important as large background signal or fluorescence limit the ability to accurately pick and assign peak positions in the subsequent steps of the binning process. Filtered spectra were binned using the peak pick and bin algorithm

with the parameters given in Table II. The sorted cluster diagrams for each sample set and the corresponding cluster assignments for each spectral file were used to identify groups of samples with similar spectra, which were used to identify samples for secondary analyses.

Table I. Raman Spectral acquisition parameters

Parameter	Setting Used
Exposure time (s)	2.0
Number of exposures	10
Laser source wavelength (nm)	785
Laser power (%)	100
Aperture shape	pin hole
Aperture size (um)	100
Spectral range	104-3428
Grating position	Single
Temperature at acquisition (degrees C)	24.0

Table II. Raman Filtering and Binning Parameters

Parameter	Setting Used
Filtering Parameters	
Filter type	Matched
Filter size	25
QC Parameters	
Peak Height Threshold	1000
Region for noise test (cm^{-1})	0-10000
RMS noise threshold	10000
Automatically eliminate failed spectra	Yes
Region of Interest	
Include (cm^{-1})	104-3428
Exclude region I (cm^{-1})	
Exclude region II (cm^{-1})	
Exclude region III (cm^{-1})	
Exclude region IV (cm^{-1})	
Peak Pick Parameters	
Peak Pick Sensitivity	Variable
Peak Pick Threshold	100
Peak Comparison Parameters	
Peak Window (cm^{-1})	2
Analysis Parameters	
Number of clusters	Variable

Procedure for Single Crystal X-Ray Diffraction

Single crystal x-ray data were collected on a Bruker SMART-APEX CCD diffractometer (M. J. Zaworotko, Department of Chemistry, University of South Florida). Lattice parameters were determined from least squares analysis. Reflection data was integrated using the program SAINT. The structure was solved by direct methods and refined by full matrix least squares using the program SHELXTL (Sheldrick, G. M. SHELXTL, Release 5.03; Siemans Analytical X-ray Instruments Inc.: Madison, WI).

The soluble crystalline forms of the present invention can be characterized, e.g., by the TGA or DSC data or by any one, any two, any three, any four, any five, any six, any seven, any eight, any nine, any ten, or any single integer number of PXRD 2-theta angle peaks or Raman shift peaks listed herein or disclosed in a figure, or by single crystal x-ray diffraction data.

EXAMPLE 1

SYNTHESIS AND ANALYSIS OF SUMATRIPTAN SUCCINATE (FORM II)

Approximately 25 microliters of an approximately 50 mg/ml solution of a sumatriptan succinate stock sample dissolved in approximately 9:1 volume:volume (v/v) water:methanol was dispersed in a 1 mL tube to form a reaction medium. The resulting reaction medium was evaporated until dry. Approximately 500 microliters of an approximately 2:1 v/v mixture of anisole and p-dioxane was added to the reaction medium and the reaction medium was heated to approximately 60 degrees C, and then rapidly cooled to approximately 5 degrees C by immersion in ice water. This heating and cooling procedure was repeated twice (cooling more slowly in the second iteration), and the tube was incubated for one to two days between cycles. The resultant sumatriptan succinate polymorph (designated as "Form II") was isolated by extracting the supernatant with a syringe, followed by drying under flowing nitrogen.

A beaker of distilled water was prepared and the pH of the water was measured. A sample of the isolated sumatriptan succinate (Form II) was dissolved in the beaker and the pH of the resulting solution was measured. The measured pH of 5.7-5.8 indicated that the sumatriptan succinate in solution was in salt form, as opposed to free base form.

To confirm the stoichiometric ratio of the sumatriptan succinate (Form II), samples were prepared with a carefully measured mass of the salt dissolved in a known volume of 85:15 v/v water:acetonitrile. This sample was characterized by HPLC, and the quantity of sumatriptan was compared to that measured from samples of the Form I polymorph (1:1) prepared similarly. The quantity of sumatriptan was determined to be the same in both forms I and II. This provides further confirmation that the material is crystalline, nonsolvated 1:1 sumatriptan succinate salt (Form II).

A sample of sumatriptan succinate Form II was examined by PXRD, using a collection time of 10 minutes. Results of this measurement are illustrated in Figures 1, and 2(a). The PXRD pattern for sumatriptan succinate Form II has a powder X-ray diffraction pattern with peaks at 2-theta angles comprising: 5.83, 13.65, 14.56, 17.63, 18.63, 20.50, 22.35, 23.29, and 24.59 degrees. Any one or a combination of any two, any three, any four, any five, or any six or more of the peaks listed above or those in the diffractogram in Figure 1.

Comparative PXRD values for sumatriptan succinate Form I are illustrated in Figure 6 and in Example 3.

DSC analysis of sumatriptan succinate form II was performed by placing 0.223 mg of sample in an aluminum pan with a press fitted pan closure, and the temperature was raised from 30 degrees C to 300 degrees C. The results of these measurements are illustrated in Figure 2. Figure 2 shows the DSC traces of both sumatriptan succinate forms I and II, where form I ("Stable Form") is the top trace and form II ("New Form") is the bottom trace. Sumatriptan succinate form II demonstrated an endothermic transition at 161 ±1.0 degrees C and a larger endothermic transition at 169 ± 1.0 degrees C.

TGA analysis of sumatriptan succinate form II was performed by placing 0.57 mg of sample in the sample pan. The starting temperature was 25 degrees C with a heating rate of 10 degrees C/minute, and the ending temperature was 300 degrees C. The results of these measurements are illustrated in Figure 3. Figure 3 shows the TGA traces of both sumatriptan succinate forms I and II, where form I ("Stable Form") is the top trace and form II ("New Form") is the bottom trace. TGA analysis confirmed that the novel sumatriptan succinate polymorph does not contain substantial amounts of either dioxane or anisole.

The results of Raman spectroscopic analysis of the sumatriptan succinate methanol polymorph are illustrated in Figure 4. Figure 4 shows the Raman spectra of both sumatriptan succinate forms I and II, where form I ("Stable Form") is the top spectrum and form II ("New Form") is the bottom spectrum. Several peaks in the Raman spectrum of the sumatriptan succinate form II are present in the spectrum of sumatriptan succinate form I, including 1549.8, 1352.5 and 1189.1 cm^{-1}. However, many characteristics of the Raman spectrum of sumatriptan succinate Form II are not present in the sumatriptan succinate form I spectrum and include, but are not limited to: 1443.4, 1410.9, 1318.4, 1308.6, 1265.1, 1235.6, 1115.0, 991.5, 942,4, and 930.7 cm^{-1}.

EXAMPLE 2

SYNTHESIS AND ANALYSIS OF SUMATRIPTAN SUCCINATE (FORM III)

An additional sumatriptan succinate polymorphic form (Form III) was prepared using a similar procedure as that described above. In order to obtain polymorphic form III of the sumatriptan succinate salt, polypropylene vials with a volume of 100 microliters were used with a normal (allowed to equilibrate at room temperature) cooling rate, and no vial treatment with a solvent or rinse. The vial was not stirred and no thermal cycling was completed. The initial sumatriptan succinate salt was dispensed in solution. It is possible to obtain form III by changing some of the parameters noted above. Table III, below, illustrates the effect of various general process parameters on the form of sumatriptan succinate that is crystallized in accordance with the instant invention.

Table III

Process Parameter	Conditions Tested	Impact on crystal form
Vial shape, combined with crystallization volume	Cylindrical, small cylinders, CMax, polypropylene Cmax: 100, 200, 500 microliters	Strong
Vial material	Glass, polypropylene	Weak
Cooling rate	Normal, quench in ice	Moderate
Vial treatment	Acetone, base rinse	Strong
Mixing rate	Stirring, no stirring	Strong
Thermal cycling	0, 1, 2 thermal cycles	Weak
Dispense method	Liquid, solid	Weak

In Table III, the terms "Strong", "Moderate" and "Weak" denote general tendencies to form sumitriptan succinate forms II or III instead of form I. Smaller vial shapes and volumes drive more efficient formation of forms II and III. A rapid cooling rate drives more efficient formation of forms II or III. Similarly, treatment of the sample vial with a solvent such as acetone or a base rinse and stirring of the salt solution both drive more efficient formation of forms II or III.

Figure 5 shows a PXRD pattern of sumatriptan succinate form III. The data are shown without the background removed. Characteristic PXRD peaks of sumatriptan succinate form III include, but are not limited to, 7.31, 14.63, 17.49, 21.05, 21.71, 22.99, and 24.01 degrees 2-theta. Any one, or any combination of any two, any three, any four, any five, or any six or more of the above peaks or of those in Figure 5 can be used to characterize sumatriptan succinate form III.

EXAMPLE 3

SUMATRIPTAN SUCCINATE FORM I

Sumatriptan succinate (classified herein as form I) was purchased from Quimica Sintetica SA (Madrid, Spain). The material was characterized by single-crystal x-ray analysis. Sumatriptan succinate form I was determined to be a member of the P21/c space group and exhibit the following single-crystal x-ray parameters: a = 9.8852 angstroms, b = 11.2255 angstroms, c = 18.649 angstroms, alpha = 90 degrees, beta = 92.796 degrees, gamma = 90 degrees.

Figure 6 shows a PXRD pattern derived from the single-crystal x-ray analysis (top) and experimental PXRD data acquired of sumatriptan succinate form I (bottom).The experimental PXRD diffractogram of sumatriptan succinate form I acquired comprises peaks at 9.14, 12.65, 13.31, 15.44, 15.74, 16.42, 19.93, 20.62, 21.38, 22.10, 22.77, and 26.96 degrees 2-theta. Any small peak shifts between the above patterns may be due to a colder temperature during single-crystal data acquisition. Figures 7A-C are packing diagrams of sumatriptan succinate form I.

EXAMPLE 4

SUMATRIPTAN SUCCINATE DICHLOROMETHANE HEMISOLVATE

400 microliters of sumatriptan succinate solution (20 mg/mL in 90:10 v/v water:methanol) was added to a cylindrical glass vial with a multipipettor. The solvent was evaporated to leave a transparent film in the vial bottom. 400 microliters of dichloromethane was added. The samples were capped and placed on a temperature-controlled hotstage at 50 degrees C for 20 minutes, then allowed to cool to room temperature overnight. Solids were isolated by removing the solvent with a pipet, and allowed to air dry.

Figure 8 shows a PXRD pattern of the dichloromethane hemisolvate of sumatriptan succinate. Characteristic PXRD peaks of sumatriptan succinate dichloromethane hemisolvate include, but are not limited to, 12.57, 13.77, 15.52, 16.79, 17.64, 19.07, 19.92, 22.06, 22.78, 23.49, 28.66, and 29.82 degrees 2-theta. Any one, or any combination of any two, any three, any four, any five, or any six or more of the above peaks or of those in Figure 8 can be used to characterize sumatriptan succinate dichloromethane hemisolvate.

DSC analysis was performed on the dichloromethane hemisolvate and the thermogram is depicted in Figure 9. In Figure 9, the top DSC trace is of the dichloromethane hemisolvate of sumatriptan succinate and the bottom trace is of sumatriptan succinate form I. The hemisolvate shows an endothermic transition near 166.7 degrees C.

TGA analysis was performed on the dichloromethane hemisolvate and the thermogram is depicted in Figure 10. In Figure 10, an approximate 9 percent weight loss is measured between room temperature and 125 degrees C.

Single-crystal data analysis was also completed on the dichloromethane hemisolvate of sumatriptan succinate. The space group was determined to be P21/c and the single-crystal parameters were as follows: a = 10.0095 angstroms, b =

12.4315 angstroms, c = 17.1489 angstroms, alpha = 90 degrees, beta = 91.478 degrees, gamma = 90 degrees.

EXAMPLE 5

SOLVATES OF SUMATRIPTAN SUCCINATE

Several solvates were made by adding specified volumes of sumatriptan succinate solution (20 mg/mL in 90:10 v/v water:methanol) to a cylindrical glass vial with a multipipettor. The solvent was evaporated to leave a transparent film in the vial bottom. The specified volume of crystallization solvent was added (500 microliters isobutanol, 50 microliters 1,4-dioxane, 50 microliters tetrahydrofuran, 500 microliters 1,2-dichloroethane), samples were capped and placed on a temperature-controlled hotstage at 50 degrees C for 20 minutes, then allowed to cool to room temperature overnight. Solids were isolated by removing a solvent with a pipet, and allowed to air dry.

An isobutanol solvate of sumatriptan succinate was prepared by the above method. PXRD analysis was completed and is found in Figure 11. PXRD peaks of the isobutanol solvate include, but are not limited to, 7.11, 14.27, 16.41, 17.25, 18.75, 21.89, and 23.19 degrees 2-theta. Any one, or any combination of any two, any three, any four, any five, or any six or more of the above peaks or of those in Figure 11 can be used to characterize sumatriptan succinate isobutanol solvate.

A 1,4-dioxane solvate of sumatriptan succinate was prepared by the above method. PXRD analysis was completed and is found in Figure 12. The data are shown without the background removed. PXRD peaks of the 1,4-dioxane solvate include, but are not limited to, 5.59, 8.79, 13.47, 14.67, 17.51, 19.49, 21.17 and 23.75 degrees 2-theta. Any one, or any combination of any two, any three, any four, any five, or any six or more of the above peaks or of those in Figure 12 can be used to characterize sumatriptan succinate 1,4-dioxane solvate.

A tetrahydrofuran solvate of sumatriptan succinate was prepared by the above method. PXRD analysis was completed and is found in Figure 13. The data are shown

without the background removed. PXRD peaks of the tetrahydrofuran solvate include, but are not limited to, 5.73, 8.87, 13.47, 14.67, 17.47, 18.67, 19.57 and 21.21 degrees 2-theta. Any one, or any combination of any two, any three, any four, any five, or any six or more of the above peaks or of those in Figure 13 can be used to characterize sumatriptan succinate tetrahydrofuran solvate.

A 1,2-dichloroethane solvate of sumatriptan succinate was prepared by the above method. PXRD analysis was completed and is found in Figure 14. The data are shown without the background removed. PXRD peaks of the 1,2-dichloroethane solvate include, but are not limited to, 5.85, 13.65, 14.61, 17.65, 18.57, 19.57, 20.56, and 22.41 degrees 2-theta. Any one, or any combination of any two, any three, any four, any five, or any six or more of the above peaks or of those in Figure 14 can be used to characterize sumatriptan succinate 1,2-dichloroethane solvate.

What is claimed is:

1. A soluble crystalline form of sumatriptan comprising:
(a) a salt comprising the reaction product of sumatriptan and an organic acid or an inorganic acid;
(b) a solvate of sumatriptan or a solvate of a salt of sumatriptan; or
(c) a polymorph of sumatriptan or a polymorph of a salt of sumatriptan.

2. The soluble crystalline form of sumatriptan of claim 1, wherein the soluble crystalline form comprises sumatriptan succinate.

3. The soluble crystalline form of sumatriptan of claim 1, comprising the reaction product of sumatriptan and an organic or inorganic acid.

4. The soluble crystalline form of sumatriptan of claim 1, wherein the soluble crystalline form of sumatriptan is a hydrate.

5. The soluble crystalline form of sumatriptan of claim 1, wherein the soluble crystalline form is an organic solvate of a sumatriptan salt formed by the reaction of sumatriptan and an organic or inorganic acid.

6. The soluble crystalline form of sumatriptan of claim 5, wherein the sumatriptan salt is sumatriptan succinate.

7. The soluble crystalline form of sumatriptan of claim 6, wherein the organic solvate is an alcohol solvate.

8. The soluble crystalline form of sumatriptan of claim 6, wherein the organic solvate is a dichloromethane hemisolvate.

9. The soluble crystalline form of sumatriptan of claim 8, wherein the hemisolvate is characterized by a powder X-ray diffraction pattern comprising peaks expressed in terms of 2-theta angles, wherein:

(a) said form is sumatriptan succinate dichloromethane hemisolvate and said X-ray diffraction pattern comprises peaks at 12.57 and 15.52 degrees;

(b) said form is sumatriptan succinate dichloromethane hemisolvate and said X-ray diffraction pattern comprises peaks at 13.77, 19.07, and 22.06 degrees;

(c) said form is sumatriptan succinate dichloromethane hemisolvate and said X-ray diffraction pattern comprises peaks at 17.63 and 22.78 degrees;

(d) said form is sumatriptan succinate dichloromethane hemisolvate and said X-ray diffraction pattern comprises a peak at 12.57 degrees;

(e) said form is sumatriptan succinate dichloromethane hemisolvate and said X-ray diffraction pattern comprises peaks at 16.79, 19.92, and 23.49 degrees; or

(f) said form is sumatriptan succinate dichloromethane hemisolvate and said X-ray diffraction pattern comprises peaks at 13.77 and 16.79 degrees.

10. The soluble crystalline form of sumatriptan of claim 8, wherein the hemisolvate is characterized by thermal analysis, wherein:

(a) said form is sumatriptan succinate dichloromethane hemisolvate and said thermal analysis comprises a DSC thermogram with an endothermic transition at about 167 degrees C; or

(b) said form is sumatriptan succinate dichloromethane hemisolvate and said thermal analysis comprises a TGA thermogram with an approximate 9 percent weight loss between about room temperature and 125 degrees C.

11. The soluble crystalline form of sumatriptan of claim 6, wherein the organic solvate is an isobutanol solvate.

12. The soluble crystalline form of sumatriptan of claim 11, wherein the solvate is characterized by a powder X-ray diffraction pattern comprising peaks expressed in terms of 2-theta angles, wherein:

(a) said form is sumatriptan succinate isobutanol solvate and said X-ray diffraction pattern comprises peaks at 7.11 and 21.89 degrees;

(b) said form is sumatriptan succinate isobutanol solvate and said X-ray diffraction pattern comprises peaks at 14.27 and 18.75 degrees;

(c) said form is sumatriptan succinate isobutanol solvate and said X-ray diffraction pattern comprises peaks at 7.11, 14.27, and 23.19 degrees;

(d) said form is sumatriptan succinate isobutanol solvate and said X-ray diffraction pattern comprises a peak at 7.11 degrees;

(e) said form is sumatriptan succinate isobutanol solvate and said X-ray diffraction pattern comprises peaks at 14.27, 16.41, and 17.25 degrees; or

(f) said form is sumatriptan succinate isobutanol solvate and said X-ray diffraction pattern comprises peaks at 17.25 and 21.89 degrees.

13. A soluble crystalline form of sumatriptan of claim 6, wherein the organic solvate is an 1,4-dioxane solvate.

14. The soluble crystalline form of sumatriptan of claim 13, wherein the solvate is characterized by a powder X-ray diffraction pattern comprising peaks expressed in terms of 2-theta angles, wherein:

(a) said form is sumatriptan succinate 1,4-dioxane solvate and said X-ray diffraction pattern comprises peaks at 13.47, 17.51, and 21.17 degrees;

(b) said form is sumatriptan succinate 1,4-dioxane solvate and said X-ray diffraction pattern comprises peaks at 5.59 and 13.47 degrees;

(c) said form is sumatriptan succinate 1,4-dioxane solvate and said X-ray diffraction pattern comprises peaks at 8.79 and 17.51 degrees;

(d) said form is sumatriptan succinate 1,4-dioxane solvate and said X-ray diffraction pattern comprises a peak at 13.47 degrees;

(e) said form is sumatriptan succinate 1,4-dioxane solvate and said X-ray diffraction pattern comprises peaks at 14.67, 19.49 and 21.17 degrees; or

(f) said form is sumatriptan succinate 1,4-dioxane solvate and said X-ray diffraction pattern comprises peaks at 13.47 and 17.51 degrees.

15. A soluble crystalline form of sumatriptan of claim 6, wherein the organic solvate is a tetrahydrofuran solvate.

16. The soluble crystalline form of sumatriptan of claim 15, wherein the solvate is characterized by a powder X-ray diffraction pattern comprising peaks expressed in terms of 2-theta angles, wherein:

(a) said form is sumatriptan succinate tetrahydrofuran solvate and said X-ray diffraction pattern comprises peaks at 5.73, 13.47, and 17.47 degrees;

(b) said form is sumatriptan succinate tetrahydrofuran solvate and said X-ray diffraction pattern comprises peaks at 8.87 and 14.67 degrees;

(c) said form is sumatriptan succinate tetrahydrofuran solvate and said X-ray diffraction pattern comprises peaks at 13.47, 17.47, and 21.21 degrees;

(d) said form is sumatriptan succinate tetrahydrofuran solvate and said X-ray diffraction pattern comprises a peak at 5.73 degrees;

(e) said form is sumatriptan succinate tetrahydrofuran solvate and said X-ray diffraction pattern comprises peaks at 17.47 and 19.57 degrees; or

(f) said form is sumatriptan succinate tetrahydrofuran solvate and said X-ray diffraction pattern comprises peaks at 5.73 and 17.47 degrees.

17. A soluble crystalline form of sumatriptan of claim 6, wherein the organic solvate is a 1,2-dichloroethane solvate.

18. The soluble crystalline form of sumatriptan of claim 17, wherein the solvate is characterized by a powder X-ray diffraction pattern comprising peaks expressed in terms of 2-theta angles, wherein:

(a) said form is sumatriptan succinate 1,2-dichloroethane solvate and said X-ray diffraction pattern comprises peaks at 5.85 and 17.65 degrees;

(b) said form is sumatriptan succinate 1,2-dichloroethane solvate and said X-ray diffraction pattern comprises peaks at 13.65, 17.65, and 18.57 degrees;

(c) said form is sumatriptan succinate 1,2-dichloroethane solvate and said X-ray diffraction pattern comprises peaks at 5.85, 13.65, and 20.56 degrees;

(d) said form is sumatriptan succinate 1,2-dichloroethane solvate and said X-ray diffraction pattern comprises a peak at 13.65 degrees;

(e) said form is sumatriptan succinate 1,2-dichloroethane solvate and said X-ray diffraction pattern comprises peaks at 14.61 and 17.65 degrees; or

(f) said form is sumatriptan succinate 1,2-dichloroethane solvate and said X-ray diffraction pattern comprises peaks at 14.61 and 22.41 degrees.

19. A soluble crystalline form of sumatriptan of claim 1, where the soluble crystalline form comprises a form selected from the group consisting of sumatriptan succinate, sumatriptan tartrate, sumatriptan citrate, sumatriptan fumarate, sumatriptan malonate,

sumatriptan maleate, sumatriptan adipate, sumatriptan di-mesylate, sumatriptan sulfate, sumatriptan benzenesulfonate, and sumatriptan phosphate.

20. A soluble crystalline form of sumatriptan of claim 1, where the soluble crystalline form is a co-crystal.

21. A soluble crystalline form of sumatriptan comprising form II or form III of sumatriptan succinate.

22. The soluble crystalline form of sumatriptan of claim 21, wherein the form is characterized by a powder X-ray diffraction pattern comprising peaks expressed in terms of 2-theta angles, wherein:

(a) said form is sumatriptan succinate form II and said X-ray diffraction pattern comprises peaks at 5.83 and 13.65 degrees;

(b) said form is sumatriptan succinate form II and said X-ray diffraction pattern comprises peaks at 14.56, 17.63, and 22.35 degrees;

(c) said form is sumatriptan succinate form II and said X-ray diffraction pattern comprises peaks at 13.65 and 17.63 degrees;

(d) said form is sumatriptan succinate form II and said X-ray diffraction pattern comprises a peak at 5.83 degrees;

(e) said form is sumatriptan succinate form II and said X-ray diffraction pattern comprises peaks at 14.56 and 18.63 degrees;

(f) said form is sumatriptan succinate form II and said X-ray diffraction pattern comprises peaks at 5.83 and 17.63 degrees;

(g) said form is sumatriptan succinate form III and said X-ray diffraction pattern comprises peaks at 7.31 and 14.63 degrees;

(h) said form is sumatriptan succinate form III and said X-ray diffraction pattern comprises peaks at 17.49 and 21.05 degrees;

(i) said form is sumatriptan succinate form III and said X-ray diffraction pattern comprises peaks at 7.31, 17.49, and 21.05 degrees;

(j) said form is sumatriptan succinate form III and said X-ray diffraction pattern comprises peaks at 14.63 and 18.15 degrees; or

(k) said form is sumatriptan succinate form III and said X-ray diffraction pattern comprises a peak at 7.31 degrees.

23. The soluble crystalline form of sumatriptan of claim 21, wherein the form is characterized by a Raman spectrum or a DSC thermogram, wherein:

(a) said form is sumatriptan succinate form II and said Raman spectrum comprises peaks at 1443 and 1264 cm^{-1};

(b) said form is sumatriptan succinate form II and said Raman spectrum comprises peaks at 1318, 1265, and 992 cm^{-1};

(c) said form is sumatriptan succinate form II and said Raman spectrum comprises peaks at 1411 and 1236 cm^{-1};

(d) said form is sumatriptan succinate form II and said Raman spectrum comprises a peak at 1265 cm^{-1};

(e) said form is sumatriptan succinate form II and said Raman spectrum comprises peaks at 1115 and 992 cm^{-1}; or

(f) said form is sumatriptan succinate form II and said DSC thermogram comprises an endothermic transition at about 161 degrees C.

24. The soluble crystalline form of sumatriptan of claim 21, further comprising an organic solvate.

25. The soluble crystalline form of sumatriptan of claim 24, wherein the organic solvate is an alcohol solvate.

26. The soluble crystalline form of sumatriptan of claim 225, wherein the alcohol is methanol, ethanol, propanol, butanol, or isobutanol.

27. A pharmaceutical dosage form comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, or 26.

28. The pharmaceutical dosage form of claim 27, wherein the dosage form may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir.

29. The pharmaceutical dosage form of claim 27, wherein the dosage form is a prodrug or a controlled release dosage form.

30. The pharmaceutical dosage form of claim 27, wherein the dosage form comprises at least one pharmaceutically acceptable excipient or diluent is an antioxidant.

31. A method of treating a migraine or related neurological disorder, comprising administering to a mammal suffering from one or more of such disorders a therapeutically effective amount of a pharmaceutical dosage form of claim 30.

32. The method of claim 31, wherein the mammal is a human.

33. A method of preventing a migraine or related neurological disorder, comprising administering to a mammal a prophylactically effective amount of a pharmaceutical dosage form of claim 27.

34. The method of claim 31, wherein

(a) the therapeutically or prophylactically effective amount is from about 10 mg to about 1000 mg per day; or

(b) the dosage form is administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir.

35. The method of claim 33, wherein

(a) the therapeutically or prophylactically effective amount is from about 10 mg to about 1000 mg per day; or

(b)the dosage form is administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir.

36. A method of altering the crystal form of a soluble crystalline form of sumatriptan by changing a parameter selected from the group consisting of vial shape/size, vial material, cooling rate, vial treatment, mixing rate, thermal cycling, and dispense method.

37. The method of altering the crystal form of a soluble crystalline form of sumatriptan of claim 36, wherein the vial shape/size is decreased.

38. The method of altering the crystal form of a soluble crystalline form of sumatriptan of claim 36, wherein the cooling rate is increased.

39. The method of altering the crystal form of a soluble crystalline form of sumatriptan of claim 36, wherein the vial is treated with a solvent or a solution.

40. The method of altering the crystal form of a soluble crystalline form of sumatriptan of claim 39, wherein the vial is treated with acetone or a base rinse.

41. The method of altering the crystal form of a soluble crystalline form of sumatriptan of claim 36, wherein the mixing rate is increased by stirring.

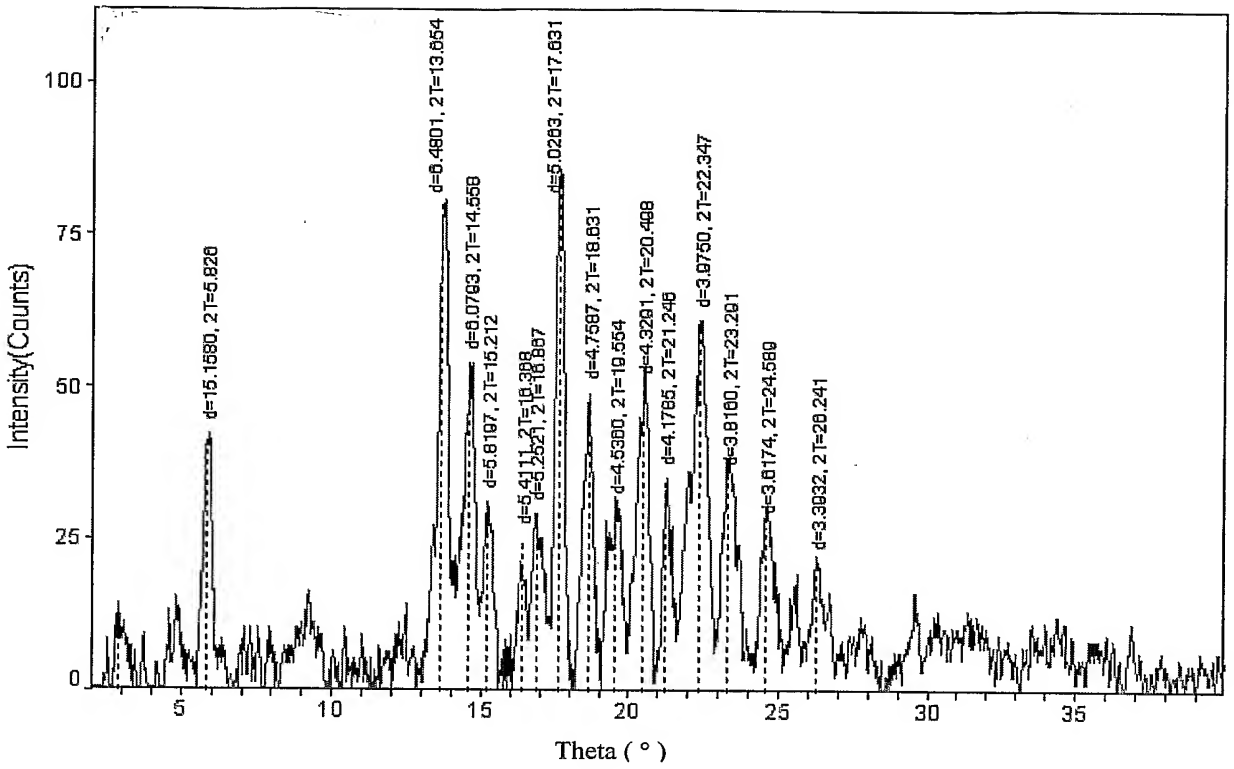


Figure 1

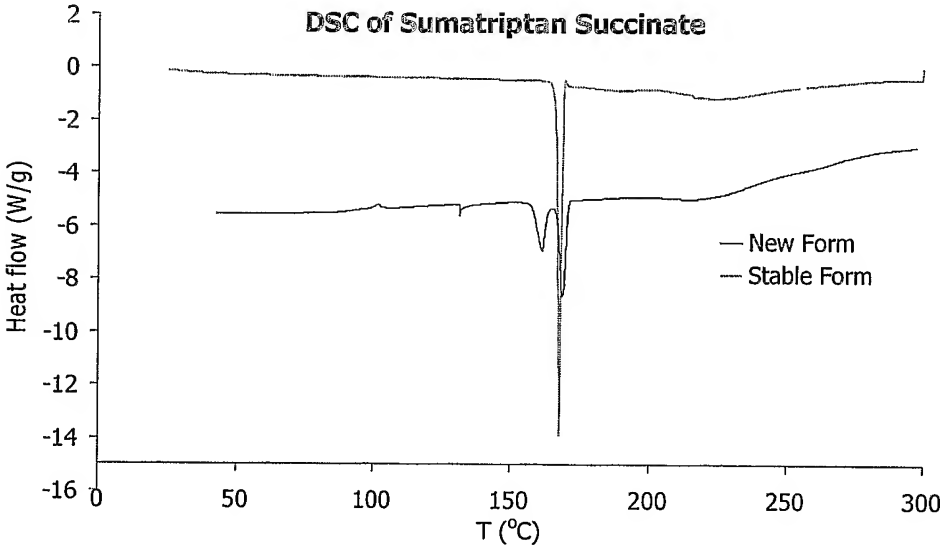


Figure 2

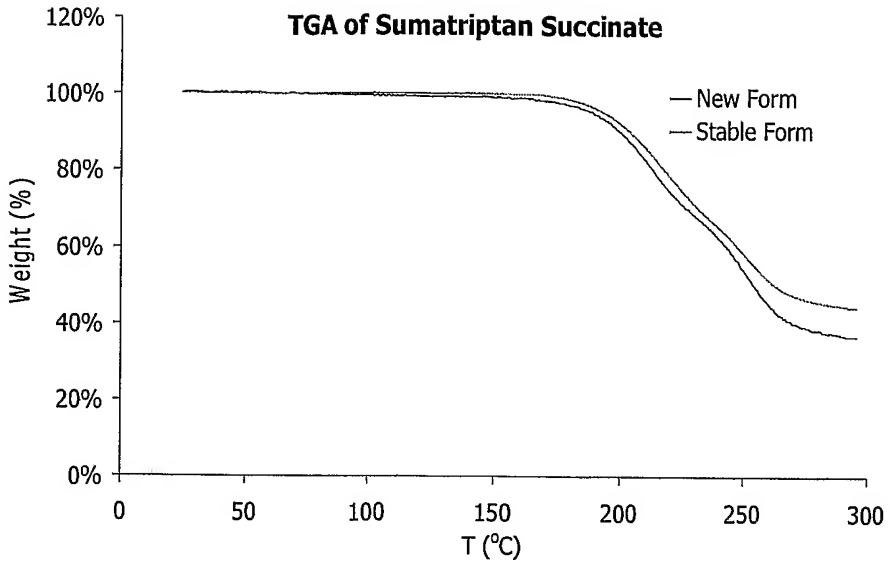


Figure 3

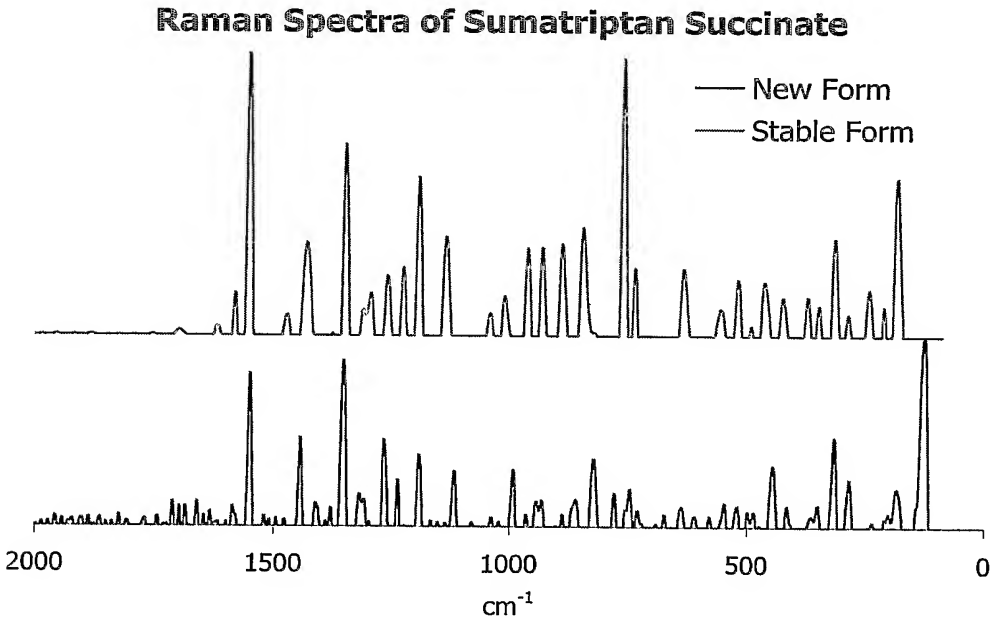


Figure 4

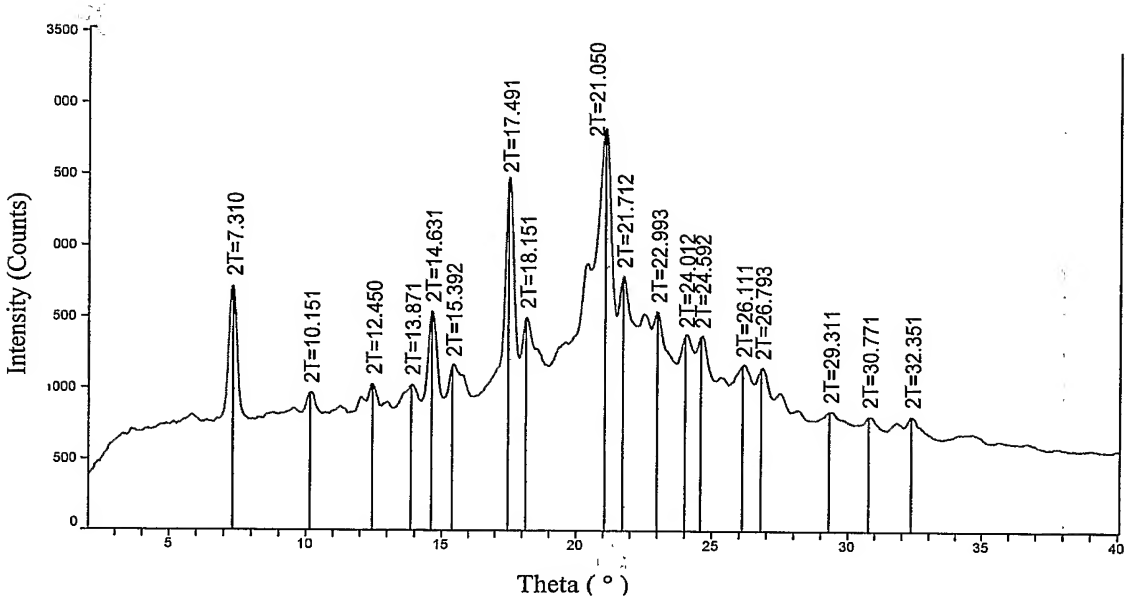


Figure 5

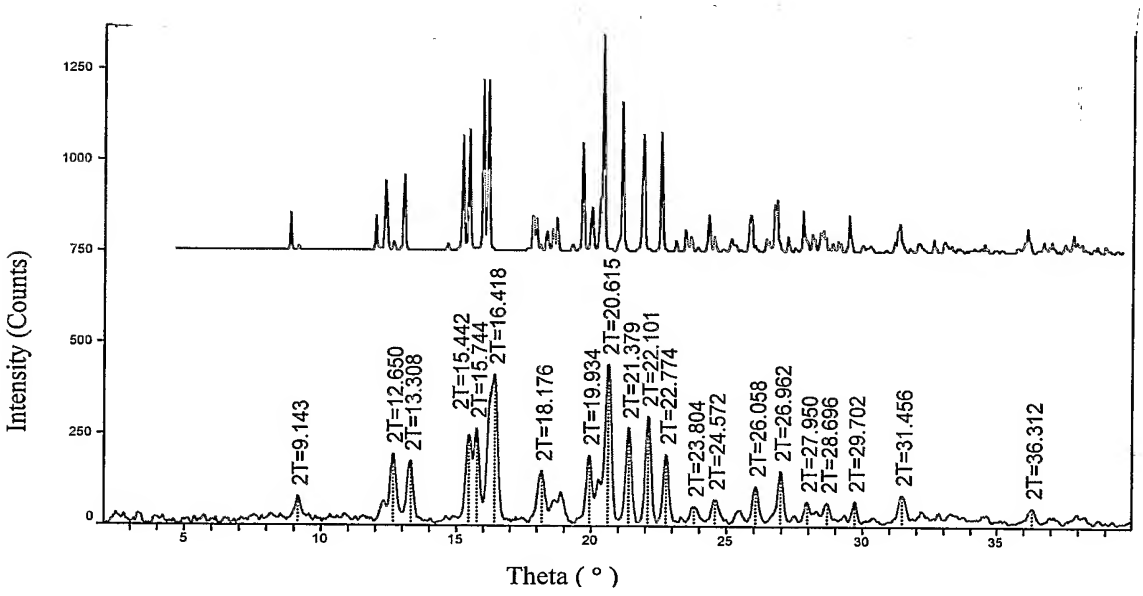


Figure 6

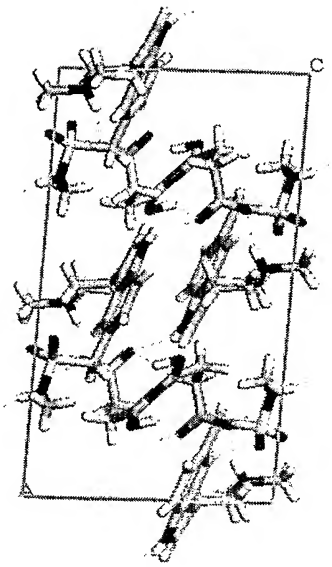


Figure 7A

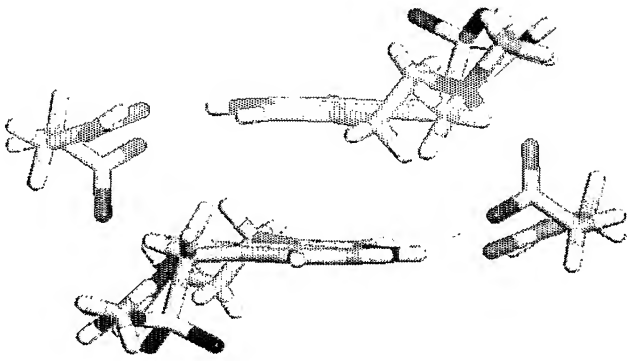


Figure 7B

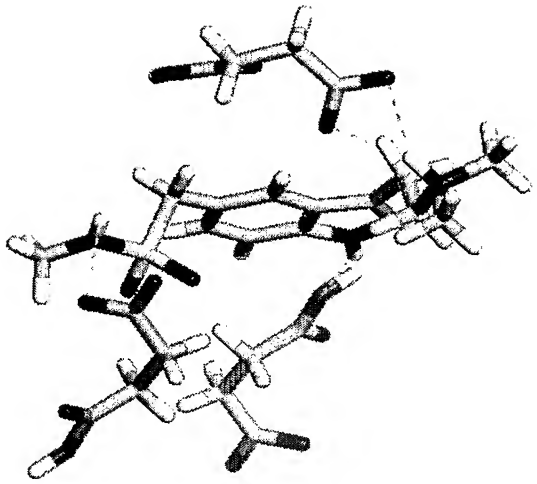


Figure 7C

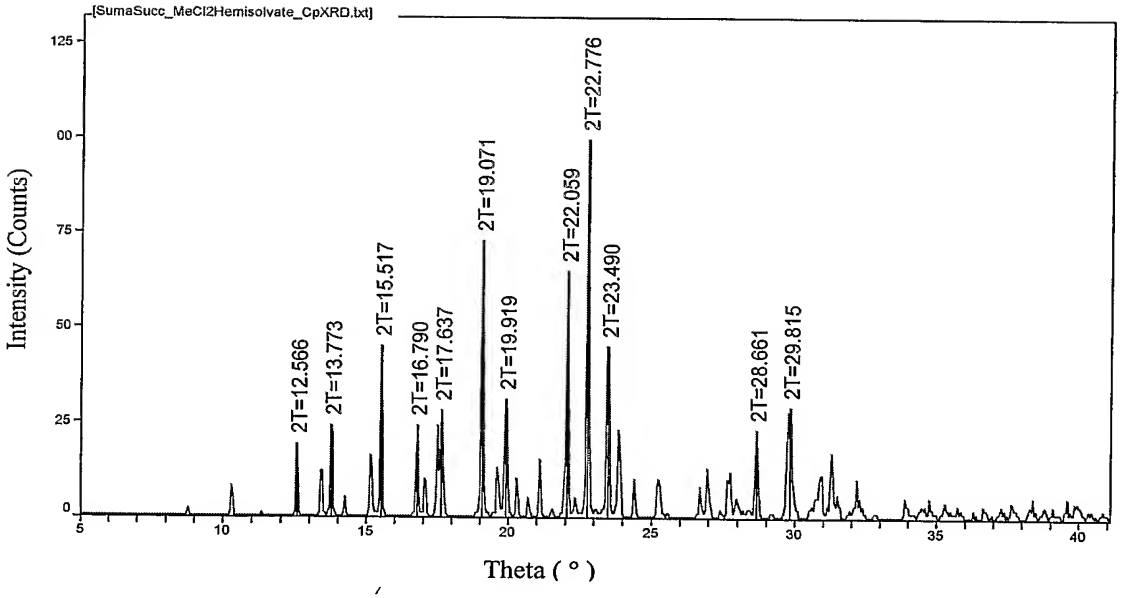


Figure 8

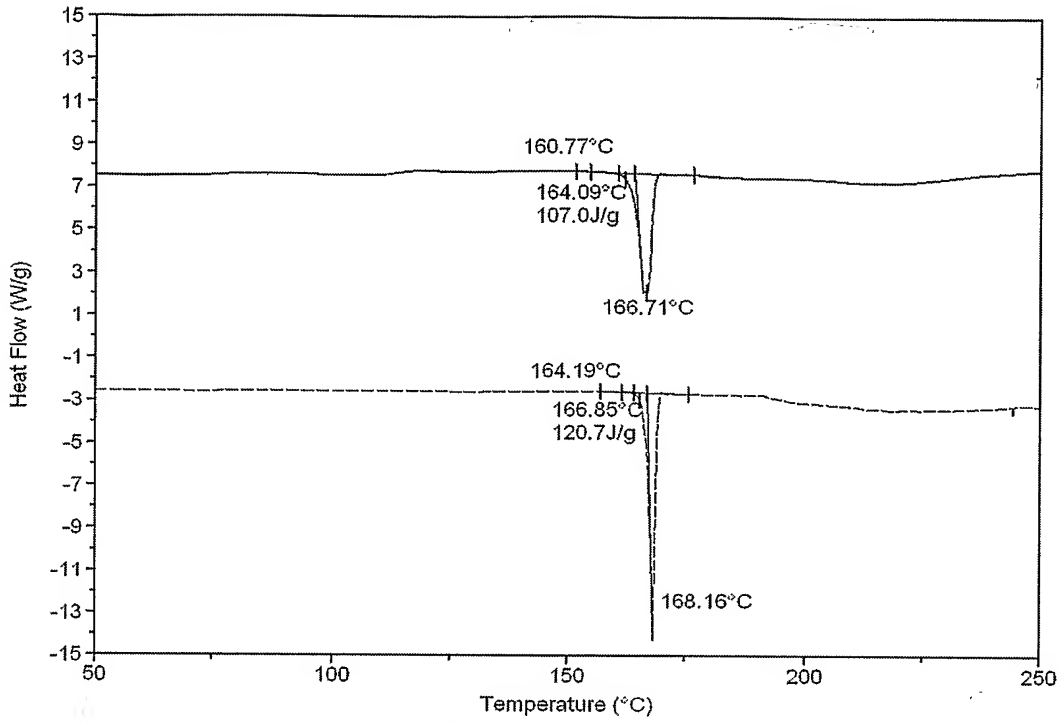


Figure 9

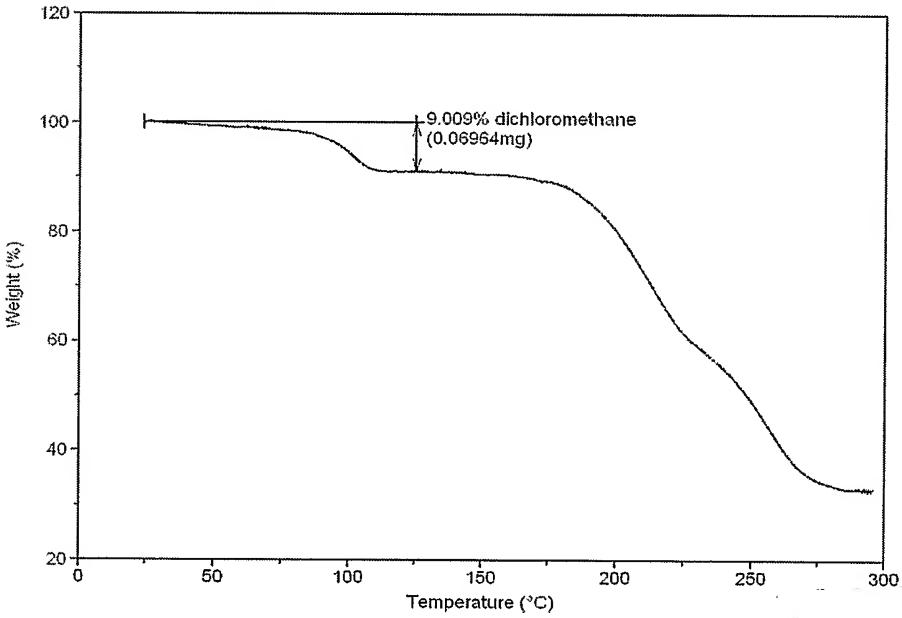


Figure 10

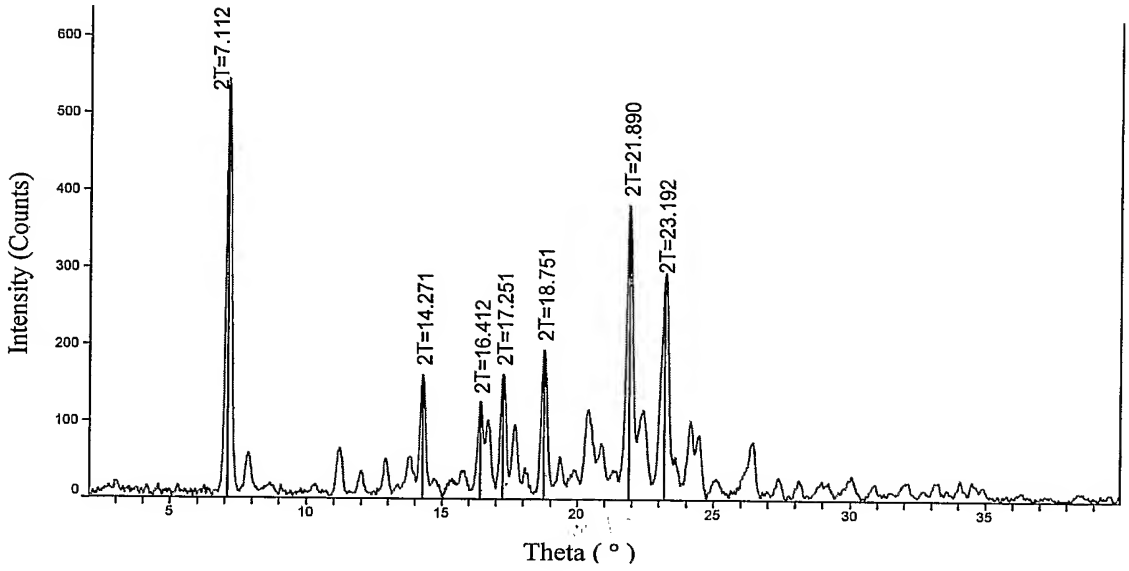


Figure 11

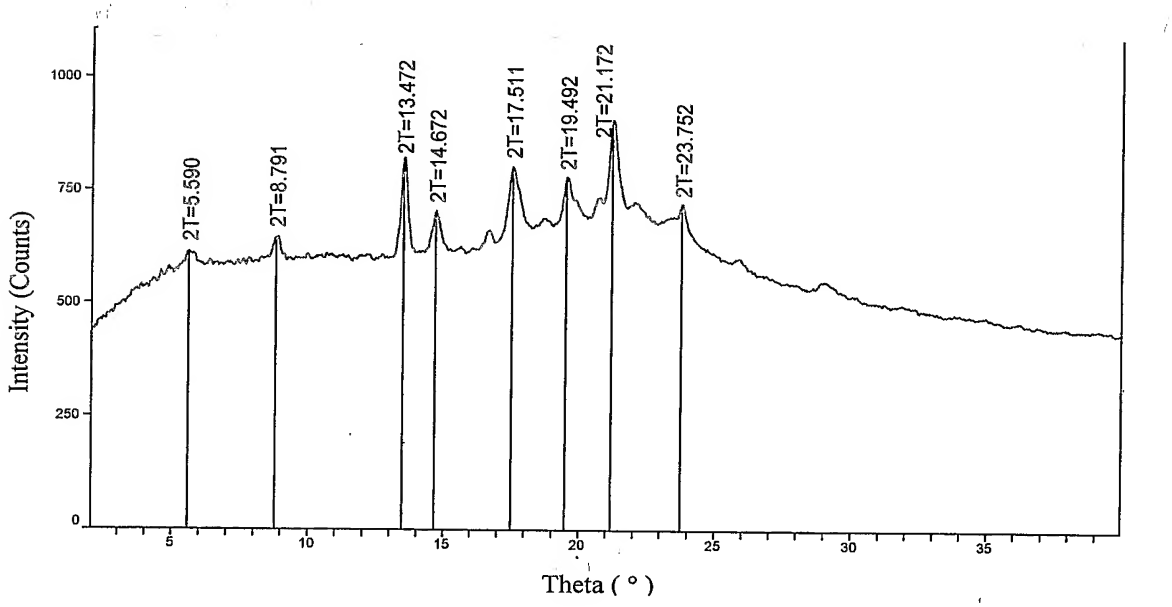


Figure 12

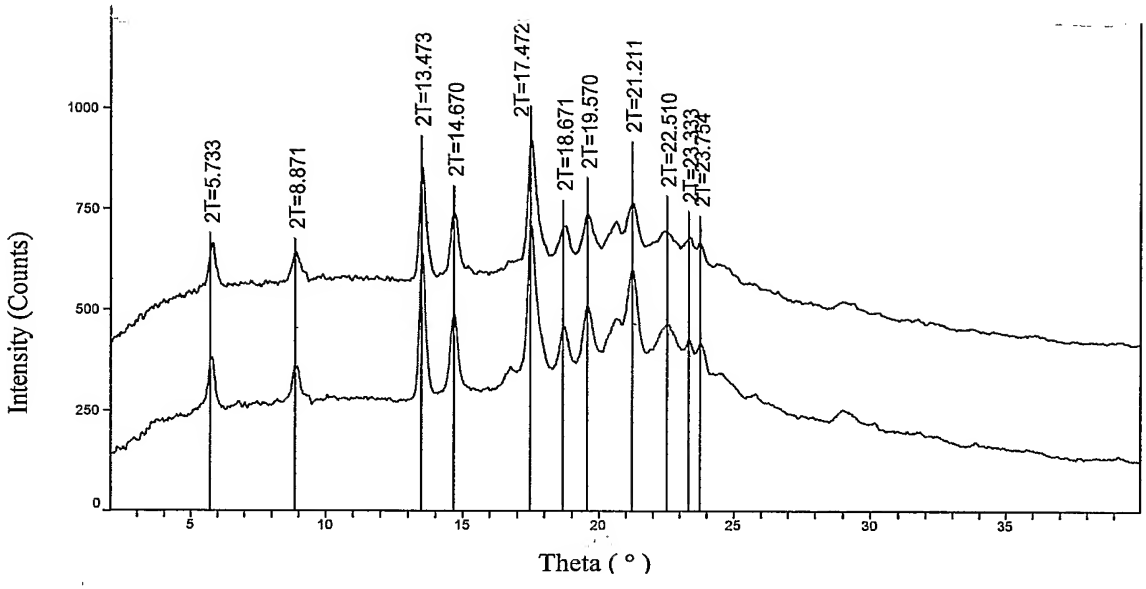


Figure 13

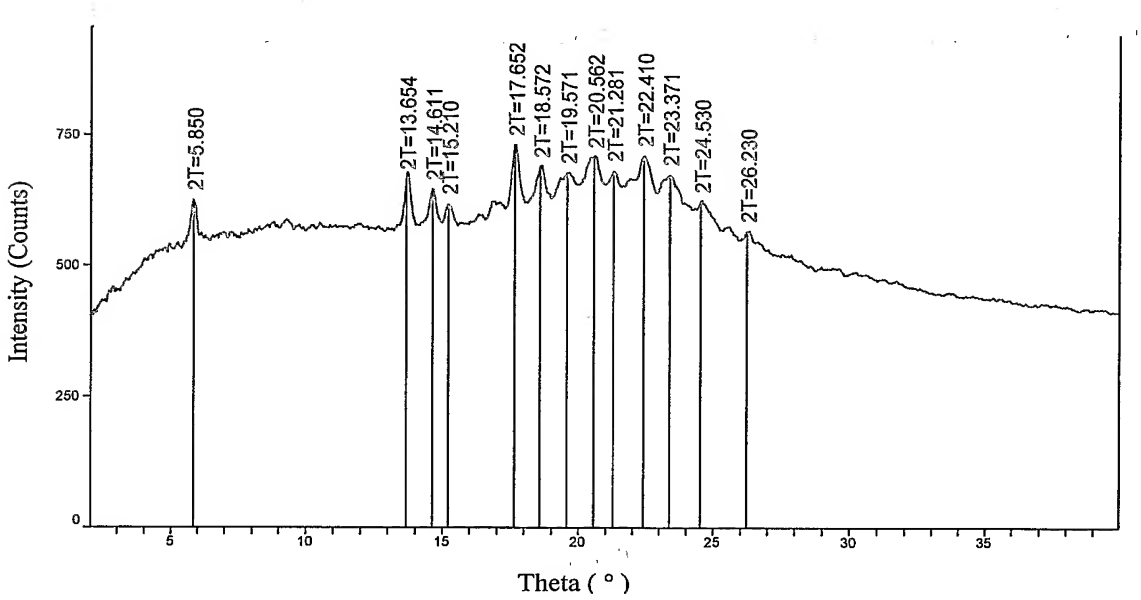


Figure 14

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/005560

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C303/40 C07C303/44 C07D209/14 C07C311/35

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 03/105836 A (RAJAN SRINIVASAN THIRUMALAI ; REDDY MANNE SATYANARAYANA (IN); MURTHY M) 24 December 2003 (2003-12-24) the whole document	1-41
P,X	US 2003/181432 A1 (LANCASTER ET AL.) 25 September 2003 (2003-09-25) *abstract; paragraph 28 and the claims*	1-41
X	EP 0 490 689 A (GLAXO GROUP LTD) 17 June 1992 (1992-06-17) the whole document	1-41
X	EP 0 503 440 A (GLAXO GROUP LTD) 16 September 1992 (1992-09-16) *abstract; page 2; page 3, lines 1 and 2; the examples and the claims*	1-41

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 July 2004	06/08/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Lorenzo Varela, M.J.

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INTERNATIONAL SEARCH REPORT

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PCT/US2004/005560

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 037 845 A (OXFORD ALEXANDER W) 6 August 1991 (1991-08-06) *examples 3-20 and the claims*	1-41
X	US 6 255 502 B1 (PENKLER LAWRENCE JOHN ET AL) 3 July 2001 (2001-07-03) *examples 1, 8, 9-11, 14, 16 and 17; tables 1 and 2 and the claims*	1-41
X	GB 2 162 522 A (GLAXO GROUP LTD) 5 February 1986 (1986-02-05) *page 1; examples 8, 16-20 and the claims*	1-41
X	US 4 816 470 A (COATES IAN H ET AL) 28 March 1989 (1989-03-28) the whole document	1-41

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2004/005560

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 31-35 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

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